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OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: **PP#8F05022.** Pyriproxyfen in/on Citrus Fruits, Fruiting Vegetables, and Tree Nuts. **HED Risk Assessment.**

DP Barcode: D249526
PRAT Case #: 290406
Submission #: S548311

CAS #: 95757-68-1
Chemical #: 129032
Class: Insecticide

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THROUGH: George F. Kramer, Ph.D, Chemist
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TO: Mark Dow/Joseph Tavano, PM#03
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Valent USA Corporation has submitted a petition for the establishment of permanent tolerances for residues of the insecticide pyriproxyfen in conjunction with a request for amended Section 3 registrations of 0.86 and 2.9 lb ai/gal emulsifiable concentrate formulations (product names: KNACK™ and ESTEEM™ Insect Growth Regulators) for use in/on citrus fruits, fruiting vegetables, and tree nuts.

A summary of the findings and an assessment of human risk resulting from the proposed uses for pyriproxyfen are provided in this document. This risk assessment is being developed to determine if permanent tolerances for pyriproxyfen residues in the raw agricultural commodities (RACs) listed above can be established. The hazard assessment was provided by William Dykstra (RAB1), the product and residue chemistry data review and dietary risk assessment by William Donovan (RAB1), the occupational/residential risk assessment by Myrta Christian

(RAB1), and the water exposure assessment by Dan Rieder and John Jordan of the Environmental Fate & Effects Division (EFED).

Summary of Findings

Revised KNACK™ and ESTEEM™ labels with specification of ground or aerial application equipment and amount of spray volume clearly indicated under Special Instructions for each pest use for almonds, citrus, and walnuts are needed. Also, the labels should be amended to specify a minimum RTI for each crop matching what was used in the crop field trials. Finally, a 30-day plantback interval for rotational crops should be added to the fruiting vegetable labels.

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I. EXECUTIVE SUMMARY

HED is conducting a risk assessment of pyriproxyfen in support of the establishment of permanent tolerances on citrus, fruiting vegetables, and tree nuts. HED has reviewed toxicology and residue data submitted by the petitioner Valent U.S.A. Corporation, on behalf of the Sumitomo Chemical Company, LTD, to support an amendment adding citrus, fruiting vegetables, and tree nuts to the KNACK™ and ESTEEM™ Insect Growth Regulator labels, and a petition to establish pyriproxyfen tolerances in/on citrus, fruiting vegetables, and tree nuts.

Pyriproxyfen was reviewed by the Hazard Identification Assessment Review Committee (HIARC) (J. Rowland, 24-OCT-1997) to evaluate the toxicology database and to address sensitivity of infants and children from exposure to this chemical. The HIARC also reassessed doses and endpoints for acute dietary, chronic dietary as well as occupational and residential risk assessments. The following dose/endpoint selections and risk assessment determinations were made:

- Acute dietary. An acute dietary dose and endpoint was not identified in the database. A risk assessment is not required.
- Chronic dietary, RfD = 0.35 mg/kg/day. (NOAEL = 35.1 mg/kg/day; Uncertainty Factor = 100)
- Short- and intermediate-term dermal. Dose and endpoints were not identified. These risk assessments are not required.
- Long-term dermal, NOAEL = 35.1 mg/kg/day. A risk assessment is required if chronic dermal exposure occurs.
- Inhalation exposure. Short- and intermediate-term inhalation exposure risk assessments are not required. For long-term inhalation exposure, the oral NOAEL of 35.1 mg/kg/day should be used.
- No additional factors required to address sensitivity of infants and children.
- No developmental neurotoxicity study was required.
- No data gaps were identified for toxicology or occupational/residential data requirements.

Based on the HIARC's recommendations, a chronic risk assessment (food, water, and residential) was performed and found not to exceed HED's level of concern. An occupational exposure assessment was not required since no endpoints of concern for short- or intermediate-term exposure were identified, and chronic occupational exposures are not expected. With the exception of the pet collar uses, consumer use of pyriproxyfen typically results in short-term, intermittent exposures. Hence, chronic residential post-application exposure and risk assessments were conducted to estimate the potential risks from pet collar uses. The risk estimates indicate that potential risks from pet collar uses do not exceed the Agency's level of concern.

The residue chemistry and toxicological data bases are adequate [subject to the label revision described in Section IV of this document] to support the following permanent tolerances for the insecticide pyriproxyfen in/on citrus fruits, fruiting vegetables (except cucurbits), and tree nuts:

Citrus Fruits	**0.30 ppm**
Fruiting Vegetables (except cucurbits)	**0.20 ppm**
Tree Nuts	**0.02 ppm**
Almond Hulls	**2.0 ppm**
Citrus Oil	**20 ppm**
Citrus Pulp, dried	**2.0 ppm**

The HED Metabolism Assessment Review Committee (MARC) determined that there are no pyriproxyfen metabolites of toxicological or regulatory concern in plants. Thus, tolerances based on the parent only are appropriate. The MARC also determined that should future crop uses increase the maximum dietary burden in animals to the point that tolerances are needed in animal commodities, the residue of concern will be pyriproxyfen and the free and sulfate forms of 4'-OH-PYR (D250953, W. Donovan, 19-NOV-1998).

II. BACKGROUND

Pyriproxyfen is identified chemically as 2-[1-methyl-2-(4-phenoxyphenoxy)ethoxy]pyridine. The technical grade of pyriproxyfen is registered as SUMILARV Technical Grade (EPA Reg. No. 10308-11). KNACK™ Insect Growth Regulator is an emulsifiable concentrate formulation containing 0.86 lb. pyriproxyfen per gallon (11.23 wt % pyriproxyfen); ESTEEM™ Insect Growth Regulator is an emulsifiable concentrate formulation containing 2.9 lb pyriproxyfen per gallon (33 wt % pyriproxyfen). Both formulations are proposed for use in/on citrus, fruiting vegetables and tree nuts. Pyriproxyfen is a reduced risk insecticide that acts by interfering with the hormonal control of insect growth and development thereby inhibiting egg hatch, larval embryogenesis, metamorphosis, and adult emergence in whiteflies. Pyriproxyfen does not control adult whiteflies directly, however, eggs laid by treated adults will not hatch. The mode of action of pyriproxyfen is completely specific to arthropods and has no relevance to vertebrate endocrine systems.

Permanent tolerances for pyriproxyfen have been established under 40 CFR 180.534 at 0.05 and 2.0 ppm on cotton seed and cotton gin byproducts, respectively (PP#6F04737, D241303 & D228499, W. Donovan, W. Dykstra, and B. Tarplee, 27-FEB-1998). Permanent tolerances are pending for pome fruits and walnuts (PP#7F04882, D251233, W. Donovan, W. Dykstra, and M. Christian, 30-DEC-1998). Previous to the cotton petition, pyriproxyfen was registered for only non-food uses. Based on plant metabolism studies conducted on cotton, apple, and tomato, the HED metabolism committee has determined that the residue of concern in plants is pyriproxyfen *per se* (D250953, W. Donovan & W. Dykstra, 19-NOV-1998).

Valent is developing KNACK™ Insect Growth Regulator (IGR) as a tool for use in insect resistance management (IRM) and integrated pest management (IPM) programs. The cotton use of KNACK™ IGR has been accepted as a Reduced Risk Pesticide candidate for accelerated review by U.S. EPA, and for simultaneous review by California EPA. Section 18 emergency exemptions for use of KNACK™ IGR on cotton for silverleaf whitefly control in Arizona were approved in 1996 (EPA File Symbol 96-AZ-06), and again in Arizona (97-AZ-06, 98-AZ-02) and California (97-CA-16, 98-CA-20) in 1997 and 1998. For all of these Section 18 actions, the time-limited tolerances for cottonseed and cotton gin byproducts were 0.05 and 2.0 ppm, respectively. Also in 1998, Section 18 emergency exemptions were approved for use of KNACK™ IGR on pears for psyllid control in Oregon (98-OR-13) and Washington (98-WA-23), on citrus in California (98-CA-09) for scale control, on tomatoes in Florida (98-FL-05) for whitefly control, and for the use of Distance Fire Ant Bait on almonds in California (98-CA-41) to control fire ants. In 1999, a Section 18 emergency exemption was approved for use of ESTEEM™ IGR on stone fruit in CA (99-CA-10) to control San Jose scale.

III. SCIENCE ASSESSMENT

A. PHYSICAL AND CHEMICAL PROPERTIES ASSESSMENT

1. Identification of Active Ingredient

Chemical Name: 2-[1-methyl-2-(4-phenoxyphenoxy)ethoxy]pyridine

Common Name: Pyriproxyfen

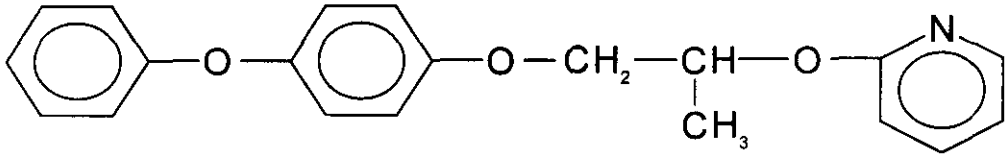
PC Code Number: 129032

CAS Registry No.: 95757-68-1

Molecular Formula: $C_{20}H_{19}NO_3$

Molecular Weight: 321.37

2. Structural Formula



3. Physical and Chemical Properties

Physical and Chemical Properties of Pyriproxyfen (SUMILARV Technical Grade)	
Physical State	Solid
Odor	Faint characteristic odor
Melting Point	47.4°C
Density	1.242 g/mL at 25°C
Solubility	0.367 mg/L in water at 25°C 7.67 g/100mL in hexane at 20°C 6.01 g/100mL in methanol at 20°C
Vapor Pressure	$<1.0 \times 10^{-7}$ mm Hg at 22.8°C
Octanol/Water Partition Coefficient	Log P_{ow} = 5.37 at 25°C
pH	6.4 at 20°C
Stability	Stable for 14 days 1) in methanol solution with Fe^{3+} or Fe, 2) at 54°C, and 3) under sunlight

B. HUMAN RISK ASSESSMENT

1. Hazard Assessment

The toxicological data base on pyriproxyfen is adequate and will support registration (HIARC: J. Rowland, 24-OCT-1997).

a. Acute Toxicity

The following table summarizes acute toxicity values and categories for pyriproxyfen:

Table 2. Acute Toxicity of Pyriproxyfen (Technical)		
GDLN	STUDY	RESULTS
81-1	Acute Oral Toxicity in Rats MRID # 42178302 Report # NNT-70-0005 Date: 2/87 Acceptable	LD_{50}: > 5000 mg/kg (both sexes) Effects: Decreased activity and diarrhea TOXICITY CATEGORY: IV
81-2	Acute Dermal Toxicity in Rabbits MRID # 42178303 Report # NNT-70-0006 Date: 2/87 Acceptable	LD_{50}: > 2000 mg/kg Not Toxic TOXICITY CATEGORY: IV
81-3	Acute Inhalation Toxicity in Rats MRID # 42178304 Report # NNT-70-0022 Date: 12/89 Acceptable	LC_{50}: > 1.3 mg/L [highest dose attainable] (four hour exposure) Decreased body weight TOXICITY CATEGORY: III
81-4	Primary Eye Irritation in Rabbits MRID # 42178305 Report # NNT-70-0022 Date: 1/87 Acceptable	Primary Irritation Score: Mild Irritant TOXICITY CATEGORY: III
81-5	Primary Dermal Irritation in Rabbits MRID # 42178306 Report # NNT-70-0022 Date: 1/87 Acceptable	Primary Irritation Score: Not an irritant TOXICITY CATEGORY: IV non-irritating to the skin under conditions of test
81-6	Dermal Sensitization in Guinea Pigs MRID # 42178307 Report # NNT-0022 Date: 1/87 Acceptable	Magnusson & Kligman method Negative sensitizing reaction

b. Subchronic Toxicity

The following table summarizes subchronic toxicity values and categories for pyriproxyfen:

Table 3. Subchronic Toxicity of Pyriproxyfen (Technical)

GDLN	STUDY	RESULTS
82-1(a)	Subchronic Feeding in Rats (13 weeks) MRID # 41321716 Report # 343-208 Date: 3/89 Guideline	Test material was administered in the diet at doses of 27.68, 141.28, 356.30, and 783.96 mg/kg/day. NOAEL: 27.68 mg/kg/day LOAEL: 141.28 mg/kg/day Effects: higher mean total cholesterol and phospholipids, decreased mean RBCs, hematocrit and hemoglobin counts and increased relative liver weight.
82-1(b)	Subchronic Feeding in Dogs (13 weeks) MRID # 42178307 Report # NNT-80-0037 Date: 5/88 Guideline	Test material was administered in the diet at doses of 0, 100, 300, and 1000 mg/kg/day. NOAEL: 100 mg/kg/day LOAEL: 300 mg/kg/day Effects: increased absolute and relative liver weight in males and hepatocellular hypertrophy in females. These findings were also observed at 1000 mg/kg/day and may represent adaptive changes at both 300 mg/kg/day and the limit dose of 1000 mg/kg/day.
82-2	21-day dermal in rats MRID # 43004102 Report # 343-244 Date: 1/93 Guideline	NOAEL for systemic effects: >1000 mg/kg/day [limit dose]. LOAEL for systemic effects was not established in this study Effects: No dermal or systemic toxicity at the limit dose.

c. Chronic Toxicity

The following table summarizes chronic toxicity values and categories for pyriproxyfen:

Table 4. Chronic Toxicity of Pyriproxyfen (Technical)		
GDLN	STUDY	RESULTS
83-1(b)	One-Year chronic feeding study in dogs MRID # 42178309 Report # 91/0776 Date: 8/91 Guideline	Test material was administered in the diet at doses of 0, 100, 300, or 1000 mg/kg/day. NOAEL: 100 mg/kg/day LOAEL: 300 mg/kg/day Effects: LOAEL: 300 mg/kg/day; based on decreased weight gain, increased absolute and relative liver weight, mild anemia, increased cholesterol and triglycerides. NOAEL: 100 mg/kg/day

d. Carcinogenicity

The following tables summarize carcinogenicity values and categories for pyriproxyfen:

Table 5. Carcinogenicity of Pyriproxyfen (Technical)		
GDLN	STUDY	RESULTS
83-2(a)	Oncogenicity study in mice MRID # 42178310 Report # 343-215 Date: 7/91 Minimum	Methods & Effects: Technical grade test material was given to male and female CD-1 mice in diet for 18 months at 0, 120, 600, or 3000 ppm (0, 18, 90, or 450 mg/kg/day, respectively). No statistically significant increase in tumor incidence relative to controls were observed in either sex at any dose up to 3000 ppm [HDT]. Systemic NOAEL = 600 ppm and systemic LOAEL = 3000 ppm based on renal lesions in males.

83-5	Chronic Feeding/ Oncogenicity study in rats MRID # 42178314 Report # 343-214 Date: 9/91 Minimum	NOAEL: 35.1 mg/kg/day LOAEL: 182.7 mg/kg/day Methods & Effects: Technical grade test material administered to male and female Sprague-Dawley rats in diet for 24 months at 0, 120, 600, or 3000 ppm (0, 7.04, 35.1, or 182.7 mg/kg/day, respectively). Decrease of 16.9% in body weight gain in females at 3000 ppm [182.7 mg/kg/day] was basis of systemic LOAEL. Systemic NOAEL is 600 ppm [35.1 mg/kg/day]. No evidence of carcinogenic response.

e. Developmental Toxicity

The following table summarizes developmental toxicity values and categories for pyriproxyfen:

Table 6. Developmental Toxicity of Pyriproxyfen (Technical)

GDLN	STUDY	RESULTS
83-3	Developmental Study in Rabbits MRID #s 42178311, 41321720 Report # NNT-80-0003 Date: 8/89 Minimum	Test material was administered by gavage at doses of 0, 100, 300, or 1000 mg/kg/day for days 6 - 18 of gestation. Maternal NOAEL: 100 mg/kg/day Maternal LOAEL: 300 mg/kg/day Effects: based on premature delivery/abortions, soft stools, emaciation, decreased activity and bradypnea. Developmental NOAEL: 300 mg/kg/day Developmental LOAEL: only 4 litters examined at 1000 mg/kg/day [HDT] without effects.

83-3	Developmental Study in Rats MRID #s 42178312, 41321719 Report # 302-2358 Date: 3/88 Minimum	Test material was administered by gavage at doses of 0, 100, 300, or 1000 mg/kg/day for days 7 - 17 of gestation. Maternal NOAEL: 100 mg/kg/day Maternal LOAEL: 300 mg/kg/day Effects: Increased incidences in mortality and clinical signs at 1000 mg/kg/day with decreases in food consumption, body weight, and body weight gain together with increases in water consumption at 300 and 1000 mg/kg/day Developmental NOAEL: 300 mg/kg/day Developmental LOAEL: 1000 mg/kg/day Effects: Increased incidences of skeletal variations and unspecified visceral variations at 1000 mg/kg/day.

f. Reproductive Toxicity

The following table summarizes reproductive toxicity values and categories for pyriproxyfen:

Table 7. Reproductive Toxicity of Pyriproxyfen (Technical)

GDLN	STUDY	RESULTS
83-4	2-Generation Reproduction Toxicity in Rats MRID # 42178313 Report # 83963 Date: 9/91 Minimum	Test material was administered in the diet at doses of 0, 100, 300, or 1000 mg/kg/day (0, 18, 87, or 453 mg/kg/day, respectively). Parental NOAEL: 1000 ppm (87 mg/kg/day) Parental LOAEL: 5000 ppm (453 mg/kg/day) Effects: based on decreased body weight, weight gain and food consumption in both sexes and both generations. Increased liver weight in both sexes of the F_1 generation and liver and kidney histopathology in F_1 males. Pup NOAEL: 1000 ppm (87 mg/kg/day) Pup LOAEL: 5000 ppm (decreased pup body weight on lactation days 14 and 21). Reproductive NOAEL = 5000 ppm [HDT]

g. Mutagenicity

The following tables summarize mutagenicity values and categories for pyriproxyfen:

Table 8. Mutagenicity of Pyriproxyfen (Technical)

GDLN	STUDY	RESULTS
84-2(a)	Gene Mutation Assay (Ames Test)/Reverse Mutation MRID # 42178315 Report # NNT-80-0034 Date: 4/88 Acceptable	Negative for induction of gene mutation measured as the reversion to histidine protrophy of 5 S. typhimurium strains and E. Coli WP2 uvra at doses from 10 to 5,000 ug/plate with & without S-9 activation. The highest dose was insoluble.
84-2(a)	Gene Mutation Assay Mammalian Cells MRID # 42178316 Report # NNT-00-0067 Date: 4/90 Acceptable	Negative for mutagenicity in Chinese hamster V79 cells with and without metabolic activation up to cytotoxic doses [300 ug/mL].
84-2(b)	Structural Chromosomal Aberration Assay In vivo cytogenetics MRID # 41321722 Report # NNT-90-0840 Date: 6/89 Acceptable	Nonclastogenic in chinese hamster ovary cells both with and without S-9 activation up to cytotoxic doses [300 ug/mL].
84-2(c)	Other Genotoxicity Assays (Unscheduled DNA Synthesis in HeLa cells) MRID # 2178317 Report # NNT-91053 Date: 7/88 Acceptable	Did not induce an increase in unscheduled DNA synthesis both with and without activation in HeLa cells exposed up to insoluble doses ranging to 6.4 ug/mL [without activation] and 51.2 ug/mL [with activation].

h. Metabolism

The following table summarizes rat metabolism values and categories for pyriproxyfen:

Table 9. Rat Metabolism of Pyriproxyfen (Technical)

GDLN	STUDY	RESULTS
85-1	Metabolism MRID # 42178318 Report # 807, 810, 811, Date: 4/88 Acceptable	Rats were orally dosed with ^{14}C-labeled pyriproxyfen at 2 or 1000 mg/kg and at repeated oral doses [14 daily doses] of unlabeled pyriproxyfen at 2 mg/kg followed by administration of a single oral dose of labeled pyriproxyfen at 2 mg/kg. Most radioactivity was excreted in the feces [81-92%] and urine [5-12%] over a 7 day collection period. Expired air was not detected. Tissue radioactivity levels were very low [less than 0.3%] except for fat. Examination of urine, feces, liver, kidney, bile and blood metabolites yielded numerous [> 20] identified metabolites when compared to synthetic standards. The major biotransformation reactions of pyriproxyfen include: 1. Oxidation of the 4' - position of the terminal phenyl group; 2. Oxidation at the 5' - position of pyridine; 3. Cleavage of the ether linkage and conjugation of the resultant phenols with sulfuric acid.

i. Neurotoxicity

Neurotoxicity has not been observed in any of the acute, subchronic, chronic, developmental or reproductive studies performed with pyriproxyfen.

j. Other Toxicological Considerations

The HIARC (J. Rowland, 24-OCT-1997) determined that a developmental neurotoxicity assessment was not required based on the following weight-of-evidence:

Pyriproxyfen does not appear to be a neurotoxic chemical. There was no indication of toxicity to the central or peripheral nervous system in subchronic or chronic toxicity studies. No

treatment-related alterations in brain weight or histopathology [non-perfused tissues] were observed following exposure to pyriproxyfen.

No evidence of developmental anomalies of the fetal nervous system were observed in the prenatal developmental toxicity studies in either rats or rabbits, at maternally toxic doses up to 1000 mg/kg/day and 300 mg/kg/day, respectively.

No evidence of an effect on functional development was observed in a postnatal segment of the developmental study in rats.

Pyriproxyfen has a complete database and no other toxicological concerns have been identified in the evaluated studies.

2. Dose/Response Assessment

a. Special Sensitivity to Infants and Children

The oral perinatal and prenatal data demonstrated no indication of increased sensitivity of rats or rabbits to *in utero and postnatal* exposure to pyriproxyfen. In the rat developmental study, the developmental NOAEL was 100 mg/kg/day and the maternal NOAEL was 100 mg/kg/day. Therefore, there was no prenatal developmental toxicity in the presence of maternal toxicity. Similarly in rabbits, the prenatal developmental NOAEL was 300 mg/kg/day and the maternal NOAEL was 300 mg/kg/day. Therefore, prenatally exposed fetuses were not more sensitive to the effects of pyriproxyfen than maternal animals. In the rat reproduction study, the parental NOAEL of 1000 ppm was identical to the pup NOAEL of 1000 ppm [and decreased body weight was seen in both pup and parental animals]. This finding demonstrates that there are no extra sensitivities with respect to pre- and post-natal toxicity between adult and infant animals. On this basis, the **10X** factor to account for enhanced sensitivity of infants and children (as required by FQPA) **was reduced to 1X by the Hazard Identification Assessment Review Committee (J. Rowland, 24-OCT-1997). This decision was affirmed during a meeting of the FQPA Committee on 07-DEC-1998.**

b. Reference Dose (RfD)

Groups of male and female Sprague-Dawley rats were fed diets containing pyriproxyfen at 0, 120, 600 or 3000 ppm (0, 7.04, 35.1, or 182.7 mg/kg/day, respectively) for 104 weeks. The NOAEL was 600 ppm (35.1 mg/kg/day) and the LOAEL was 3000 ppm (182.7 mg/kg/day) based on a 16.9% decrease in body weight gain in females when compared to controls. In males the NOAEL was greater than or equal to 183 mg/kg/day, the highest dose tested. Although the highest dose tested in males did not cause any toxicity and the toxicity predicted in the 90 day study did not materialize in the long-term study, the RfD Committee concluded that repeating this study at higher doses would not provide additional information on either chronic toxicity or on the carcinogenic potential of pyriproxyfen. Furthermore, a LOAEL was established in females.

In a subchronic study, male and female Sprague-Dawley rats were fed diets containing pyriproxyfen at 0, 400, 2,000, 5,000 or 10,000 ppm for 90 days. These doses were equivalent to 0, 23.49, 117.79, 309.05, or 641.8 mg/kg/day in males and 0, 27.68, 141.28, 356.30, or 783.96 mg/kg/day in females, respectively. The NOAEL was 23.49 mg/kg/day in males and 27.68 mg/kg/day in females based on higher mean total cholesterol and phospholipids, decreased mean RBCs, hematocrit, and hemoglobin counts, and significantly higher relative liver weights at the LOAEL of 117.79 mg/kg/day in males and 141.28 mg/kg/day in females. This study is considered supportive of the two year study.

The NOAEL for systemic toxicity from the 2-year rat study was 35.1 mg/kg/day and the LOAEL was 141.38 mg/kg/day. An uncertainty factor (UF) of 100 was applied to account for inter-(10X) and intra-(10X) species variation. The **10X** factor to account for enhanced sensitivity of infants and children (as required by FQPA) **was reduced to 1X, since there was no special sensitivity for infants and children.** For chronic dietary risk assessment, **a UF of 100 is adequate** for the protection of this subpopulation from exposure to pyriproxyfen. A UF of 100 is adequate because:

(i) Developmental studies showed no increased sensitivity in fetuses as compared to maternal animals following **in utero** exposures in rats and rabbits.

(ii) A two generation reproduction toxicity study in rats showed no increased sensitivity in pups as compared to adults.

(iii) The toxicology data base is complete and there are no data gaps.

Consequently, the RfD is 0.35 mg/kg/day.

c. Carcinogenic Classification

Pyriproxyfen is classified as Category E: not carcinogenic in two acceptable animal studies.

d. Developmental and Reproductive Toxicity

The oral rat and rabbit developmental studies and the oral rat reproduction study demonstrated no indication of increased sensitivity of rats or rabbits to *in utero and postnatal* exposure to pyriproxyfen.

In a prenatal developmental toxicity study in Sprague-Dawley rats, pyriproxyfen was administered at doses of 100, 300, or 1000 mg/kg/day by gavage in 5 mL/kg of corn oil on gestation days 7 - 17. The study was conducted in two segments. In one, the dams were killed on gestation day 21 and the fetuses were evaluated. In the other, the dams delivered naturally and pups were weaned at postnatal day 21. Pups were killed serially at postnatal day 21 (after assessment of reflexes and sensory response), at 8 weeks of age [following open field testing, rotorod testing, and examination of learning ability in a water maze], or after assessment of

reproductive performance. The maternal NOAEL was 100 mg/kg/day, based upon decreased body weight, body weight gain, and food consumption, and increased water consumption at the LOAEL of 300 mg/kg/day. At 1000 mg/kg/day, increased incidences of mortality and clinical signs were also observed. The developmental NOAEL was 300 mg/kg/day, based on the incidence of skeletal variations at gestation day 21 and unspecified visceral variations at postnatal day 56.

A prenatal developmental toxicity study was conducted in pregnant JW-NIBS rabbits, in which pyriproxyfen was administered by gavage at doses of 100, 300, or 1000 mg/kg/day in distilled water on gestation days 6-18. The maternal NOAEL was 100 mg/kg/day. The maternal LOAEL was 300 mg/kg/day, based on the occurrence of premature delivery/abortion, soft stools, emaciation, lusterless fur, decreased activity, and bradypnea/deep breathing. At 1000 mg/kg/day, these signs increased in incidence and frequency. The developmental NOAEL was 300 mg/kg/day. The committee recommended that the abortions be considered evidence of toxicity to the fetuses, and that the developmental LOAEL be set at 1000 mg/kg/day, in spite of the overwhelming maternal toxicity.

In a two-generation reproduction study, pyriproxyfen was administered to Sprague-Dawley rats at dietary levels of 200, 1000, or 5000 ppm [18, 87, or 453 mg/kg/day for males and 20, 96, or 498 mg/kg/day for females]. The parental NOAEL for both sexes was 1000 ppm and the parental NOAEL was 5000 ppm, based on decreased body weights, body weight gains, and food consumption in both sexes and generations, increased liver weight in F1 male and females, and histopathological changes in the liver and kidney of F1 males. The reproductive NOAEL was 5000 ppm. The pup NOAEL was 1000 ppm and the LOAEL for pups was 5000 ppm, based on decreased body weights on lactation days 14 and 21.

e. Dermal Absorption

A dermal absorption study was not available for evaluation. Therefore, the HIARC estimated a dermal absorption rate of **no more than 10% percent** based on the interpretation of data from oral and dermal studies in rats.

In the oral developmental toxicity study in rats, the NOAEL was 100 mg/kg/day based on decreased body weight, body weight gain, and food consumption and increased water consumption at 300 mg/kg/day (LOAEL).

In the dermal toxicity study in rats, no dermal or systemic toxicity was observed at the Limit-Dose of 1000 mg/kg/day.

In extrapolating from oral to dermal route, the HIARC made the following assumptions: 1) that the toxicity seen via the oral route is due to direct transport of pyriproxyfen from the absorption site to the target organs and 2) that metabolism following oral and dermal routes are similar. Under these assumptions, no more than 10% (oral dose of 100 mg/kg/day / dermal dose 1000

mg/kg/day x 100) of pyriproxyfen applied to the rat skin is absorbed without effects. (J. Rowland, 24-OCT-1997).

f. Other Toxicological Endpoints

i. Acute Dietary (1 day)

An acute dietary endpoint and dose was not identified in the toxicology data base by HIARC (14-OCT-1997). This risk assessment is not required.

ii. Short- and Intermediate-Term Occupational and Residential Exposure

No dermal or systemic toxicity was observed in the 21-day dermal toxicity study at the limit-dose of 1000 mg/kg/day. In addition, there were no effects observed in oral toxicity studies including the developmental toxicity studies in rats and rabbits that could be expected to occur during this time period [1 - 7 days]. Therefore, an endpoint was not identified for this risk assessment. This risk assessment is not required.

iii. Chronic Occupational and Residential (Non-Cancer)

There was a 28-day inhalation study for pyriproxyfen (MRID # 42178308), but because of the lack of significant effects, no assessment was required. The HIARC recommended that the chronic oral NOAEL of 35.1 mg/kg/day be used together with a 10% dermal absorption value, a 100% inhalation absorption value, and a MOE requirement of 100 for long-term dermal and inhalation exposure. The HIARC selected an oral NOAEL of 35.1 mg/kg/day [see RfD] for this risk assessment because of the: 1) lack of appropriate inhalation studies, 2) potential for long-term exposure via this route, and 3) recommendation of a 10% dermal absorption value for chronic dermal exposure.

iv. Margin of Exposure for Occupational/Residential Exposures

A Margin of Exposure of 100 is adequate to ensure protection from occupational and residential exposures to pyriproxyfen by dermal and inhalation routes. An MOE of 100 is adequate because:

(i) Developmental toxicity studies showed no increased sensitivity to fetuses as compared to maternal animals following in utero exposures in rats and rabbits.

(ii) A two generation reproduction toxicity study in rats showed no increased sensitivity to pups as compared to adults.

(iii) The toxicology data base is complete and there are no data gaps.

3. Dietary Exposure and Risk Assessment/Characterization

a. Dietary Exposure (Food Source)

i. Directions for Use

The petitioner provided specimen labels for a 0.86 lb/gal emulsifiable concentrate (EC) formulation (product name: KNACK™ Insect Growth Regulator) and a 2.9 lb/gal EC (product name: ESTEEM™ Insect Growth Regulator) including proposed uses on almond, citrus, tomato, pepper, and walnuts. The proposed use patterns are described below.

Citrus Fruits: Both ECs are proposed for multiple foliar applications to citrus fruits at up to 50 g ai/A/application (0.11 lb ai/A/application). The label allows a maximum of three applications per year, and specifies a maximum use rate of 150 g ai/A/season (0.33 lb ai/A/season). The proposed labels specify a 1-day preharvest interval (PHI), but do not indicate a minimum retreatment interval (RTI). The submitted crop field trial data support a 21-day RTI. Applications are to be made in 200-1500 gal of water/A, and oils may be added to the spray volume according to manufacturer specified rates (quantity unspecified). The labels do not specify the type of application equipment allowed.

Fruiting Vegetables (peppers and tomatoes): Both ECs are proposed for multiple foliar applications to peppers and tomatoes at 20-30 g ai/A/application (0.04-0.07 lb ai/A/application). The label allows a maximum of three applications per year, and specifies a maximum use rate of 80 g ai/A/season (0.18 lb ai/A/season). The proposed labels specify a 14-day PHI, but do not indicate a minimum RTI. The submitted crop field trial data support a 14-day RTI. Applications are to be made using ground equipment in 10-150 gal of water/A.

Tree Nuts (almonds and walnuts): Both ECs are proposed for multiple foliar applications to almonds and walnuts at 40-50 g ai/A/application (0.09-0.11 lb ai/A/application) for early and late season insect control. The labels specify a maximum use rate of 150 g ai/A/season (0.33 lb ai/A/season), implying a maximum number of three applications allowed each season. The proposed labels specify a 21-day PHI; however, a minimum RTI is not indicated. The submitted crop field trial data support a 14-day RTI. Applications are to be made in 100-400 gals/A; however, the type of application equipment (ground or aerial) is not specified on the labels. The use directions for walnuts allow the addition of oil at 1-2% to the spray mixture. The labels for almonds also allow the application of pyriproxyfen with spray oil using manufacturer specified rates (quantity unspecified).

Conclusions: The proposed use directions for the 0.86 and 2.9 lb ai/gal ECs are inadequate. The labels should be amended to specify a minimum RTI for each of the crops. The proposed labels for almonds, citrus, and walnuts should be amended to specify the type of application equipment (ground or aerial equipment) allowed. In addition, for almonds and citrus, the labels should specify the quantity of spray oil that may be added to the final spray volume. A revised Section B should be submitted.

ii. Nature of the Residue - Plants

The nature of the residue in plants is understood. Acceptable metabolism studies using [^{14}C]-labeled pyriproxyfen (phenyl and pyridyl rings) have been performed in/on apples (PP#7F04882, D238190, W. Donovan, 07-DEC-1998), cotton (PP#6F04737, D228556, J. Garbus & R.W. Cook, 06-MAY-1997), and tomatoes (PP#8F05022, D253836, W. Donovan, 25-MAR-1999). Metabolism of pyriproxyfen in apples proceeds through hydroxylation and cleavage of the phenoxy ether linkage. Primary metabolites formed are further metabolized to more polar products by oxidation or conjugation reactions. Similar metabolic pathways were observed for the metabolism of pyriproxyfen in cotton and tomatoes.

Accordingly, the HED Metabolism Assessment Review Committee (MARC) has determined that there are no pyriproxyfen metabolites of toxicological or regulatory concern in plants (D250953, W. Donovan, 19-NOV-1998). Thus, tolerances based on the parent only are appropriate.

iii. Nature of the Residue - Animals

Poultry
There are no poultry feed items associated with citrus, fruiting vegetables, or tree nuts. Therefore, no secondary residues are expected to occur in poultry eggs, fat, meat, and meat byproducts as a result of the proposed uses on citrus, fruiting vegetables, and tree nuts.

Ruminants
Valent submitted data from studies (MRID #s 44036922 and 44036923) investigating the metabolism of [Ph-^{14}C uniformly ring labeled] and [Py-^{14}C in pyridine ring 2 and 6 positions] pyriproxyfen in lactating goats. This study was previously reviewed in a memo dated 06-MAY-1997 (DP Barcode D228556, J. Garbus & R.W. Cook). Two goats were fed 10 ppm of Ph-^{14}C pyriproxyfen daily for 5 days, while two other goats were fed 10 ppm of Py-^{14}C pyriproxyfen daily for 5 days, with 1 control goat. Urine, feces and milk samples were obtained twice daily. After sacrifice at 6 hours after last dose, samples of blood, heart, kidneys, liver, loin muscle, rear leg muscle, omental and perirenal fat, gastrointestinal tract and contents were collected for ^{14}C analysis.

The majority (62-76%) of the ^{14}C-pyriproxyfen ingested by goats was excreted in urine and feces, with residue levels in feces being higher than in urine. Approximately 25 to 32% of the administered ^{14}C-pyriproxyfen was found in goat tissues, with the large majority located in the gastrointestinal tract. These studies show that metabolism of phenyl-^{14}C pyriproxyfen in goats proceeds through hydroxylation of the phenoxyphenyl and pyridyl rings, sulfation of the 4'-OH phenoxyphenyl moiety, and cleavage of the ether linkage. Metabolism of pyridyl-^{14}C pyriproxyfen in goats proceeds through hydroxylation of the phenoxyphenyl and pyridyl rings, sulfation of the 4'-OH phenoxyphenyl moiety, cleavage of the ether linkage and oxidation of the side chain. HED concludes that the nature of the residue in ruminants is adequately understood.

The HED MARC determined that the residues of concern in animals are pyriproxyfen and the free and sulfate forms of 4'-OH-PYR (D250953, W. Donovan, 19-NOV-1998).

iv. Residue Analytical Methods

In support of PP#6F04737, residue analytical method RM-33P-2 (cotton) underwent validation in EPA laboratories (A.J. Krynitsky, 27-MAR-1997) and is suitable to gather residue data and to enforce tolerances (PP#6F04737, D235563, R. Cook, 30-APR-1997).

For data collection and tolerance enforcement in fruits, Valent has proposed use of Method RM-33P-1-3, "Determination of Pyriproxyfen and 4'-OH-Pyriproxyfen Residues in Apples, Pear, and Citrus Fruit". This method was successfully validated by an independent laboratory on the first try as reported in MRID 44329507. The mean percent pyriproxyfen recoveries were 79.4 ± 1.6% and 84.9 ± 4.7% on apples and oranges, respectively. This method differs significantly from the method used to analyze cotton seed. Accordingly, method RM-33P-1-3 underwent validation in EPA laboratories (A.J. Krynitsky and D.M. Swineford, 21-JUN-1999) and is suitable to gather residue data and to enforce tolerances (D257337, W. Donovan, 01-JUL-1999). As described previously (D238190, W. Donovan, 07-DEC-1998), this method also underwent successful radiovalidation using apple pomace samples. Thus, Valent has adequately demonstrated the extraction efficiency of this analytical method.

For data collection and tolerance enforcement in nutmeats, Valent has proposed use of Method RM-33N-2. This method is largely similar to Method RM-33P-1-3; thus, no independent laboratory validation was conducted for this method. However, method RM-33N-2 underwent validation in EPA laboratories (A.J. Krynitsky and D.M. Swineford, 21-JUN-1999) and is suitable to gather residue data and to enforce tolerances (D257337, W. Donovan, 01-JUL-1999). Method RM-33H was also validated in EPA laboratories (A.J. Krynitsky and D.M. Swineford, 21-JUN-1999) and found suitable to gather residue data and enforce tolerances in almond hulls (D257337, W. Donovan, 01-JUL-1999).

For data collection and tolerance enforcement in fruiting vegetables, Valent has proposed use of Method RM-33P-9. This method is largely similar to Method RM-33P-1-3; thus, no independent laboratory validation was conducted for this method. However, method RM-33P-9 underwent validation in EPA laboratories (A.J. Krynitsky and D.M. Swineford, 21-JUN-1999) and is suitable to gather residue data and to enforce tolerances (D257337, W. Donovan, 01-JUL-1999).

v. Multiresidue Methods

Valent submitted data from a study performed by Corning Hazleton Inc. (MRID # 44036926) describing the testing of pyriproxyfen through the Food and Drug Administration (FDA) Multiresidue Methods Protocols A, C, D, E, and F found in the Pesticide Analytical Manual Volume I (PAM I), Appendix II. This study was previously reviewed in a memo dated 06-MAY-1997 (D228556, J. Garbus & R.W. Cook). Pyriproxyfen was recovered from fortified apple and cotton samples through protocols A, C, D, E, and F. The metabolite PYPAC was tested with protocols A, B, C, and D. The multiresidue methods will serve as confirmatory methods for residues of pyriproxyfen. The multiresidue recovery data were sent to the FDA for inclusion in PAM I (R.W. Cook, 24-JAN-1997).

vi. Storage Stability Data

A stability study of pyriproxyfen on cotton RACs in frozen storage was previously reviewed (D228556, J. Garbus & R.W. Cook, 06-MAY-1997). Similarly, the stability studies of pyriproxyfen on apples, apple processed commodities, walnuts, and animal commodities were previously reviewed (D238190, W. Donovan, 07-DEC-1998). The data were found to be adequate to conclude that decline in frozen storage does not occur during the intervals that the samples were stored.

In conjunction with the residue studies on almonds, citrus, and fruiting vegetables (MRIDs 446301-02 through -07), the petitioner conducted studies depicting the stability of residues of pyriproxyfen and its metabolites in crop matrices stored at -20°C. Control samples of almond hulls, oranges, peppers, and tomatoes were fortified with pyriproxyfen and either 4'-OH-PYR or PYPA each at 0.10 ppm and analyzed periodically at frozen storage intervals up to a maximum of 91-280 days. An additional short-term (1 month) study with weekly sampling intervals was conducted on tomato to verify the results of the long-term study. At each sampling interval, a freshly fortified and two stored fortified samples were analyzed using GC/NPD and HPLC/FLD methods. Apparent residues of each analyte were <0.01 ppm ($<$ LOD) in controls with the exception of one orange control sample which bore residues of 4'-OH-PYR at 0.015 ppm. Recoveries were corrected for residues in control samples by the petitioner.

The storage stability data are adequate and indicate that residues of pyriproxyfen *per se* are stable frozen (-20°C) in almond hulls and oranges for up to 4 months, and are relatively stable in peppers for up to 3 months. Residues of pyriproxyfen in tomato declined by ~25% within one week, and by 40-60% after 1 month of frozen storage.

Residues of 4'-OH-PYR appeared to decline by ~25% after 1 month of storage in almond hulls, but were relatively stable for up to 4 months of storage at -20°C. Residues of 4'-OH-PYR were stable in oranges after 3 months of frozen storage at -20°C. Residues of PYPA were stable in tomato and peppers after 3 months of storage, but showed an apparent loss of ~35% in tomato after 9 months at -20°C.

Previously reviewed storage stability data (PP#7F04882, DP Barcode D238190, W. Donovan, 07-DEC-1998) indicates that pyriproxyfen and 4'-OH-PYR are stable in walnut nutmeat at -20°C for up to 3 months.

<u>*Conclusions*</u>: The submitted storage stability data are adequate and indicate that pyriproxyfen is stable at -20°C for up to 4 months in almond hulls and oranges, and for up to 3 months in peppers. In tomato, pyriproxyfen residues declined by ~25% within one week, and by ~40-60% after 1 month of frozen storage at -20°C; however, with the exception of two trials, tomato residue samples were analyzed within approximately one week of sampling. The maximum frozen storage interval from sampling to analysis for almond, citrus, and pepper was $<$ 1-3 months. These data, together with previously submitted data indicating that residues of pyriproxyfen are stable in frozen walnut nutmeat for 3 months, adequately support the residue

data submitted for the permanent tolerance petitions for citrus, fruiting vegetables, and tree nuts.

The submitted storage stability data, together with existing storage stability data on walnuts, indicate that residues of 4'-OH-PYR and PYPA are relatively stable in almonds and oranges, and tomato and peppers, respectively, over the storage intervals and conditions reflected in the residue studies (≤3 months at ~-20°C).

vii. Crop Field Trials

Citrus Fruits Group

Oranges

Valent submitted data from 13 field trials conducted in CA (3), FL (9), and TX (1) during 1995-1998 depicting residues of pyriproxyfen in/on oranges (MRID 44630105). These studies were reviewed and found to be acceptable (D253836, W. Donovan, 25-MAR-1999).

Pyriproxyfen residues were 0.05-0.23 ppm in/on 26 orange samples harvested 1 day after the last of three applications at 1x. At 2x, pyriproxyfen was detected at 0.36-0.41 ppm in/on four samples. In decline studies, residues decreased ~33% in one field trial and remained relatively constant in three others from 1-21 days posttreatment. The results of the separate analysis of two samples of orange peel and interior flesh from oranges treated at a 1x or 2x rate indicate that residues of pyriproxyfen and 4'-OH-PYR are found primarily in the peel.

Lemons

The petitioner submitted data from 6 field trials conducted in AZ, CA (4), and FL during 1996-1997 depicting residues of pyriproxyfen in/on lemons (MRID 44630106). These studies were reviewed and found to be acceptable (D253836, W. Donovan, 25-MAR-1999).

Pyriproxyfen residues were <0.01-0.24 ppm in/on 12 lemon samples harvested 1 day after the last of three applications at 1x. At 2x, pyriproxyfen was detected at 0.55 and 0.58 ppm in/on two treated samples.

Grapefruit

Valent submitted data from 7 field trials conducted in CA (3), FL (3), and TX (1) during 1996 and 1997 depicting residues of pyriproxyfen in/on grapefruit (MRID 44630104). These studies were reviewed and found to be acceptable (D253836, W. Donovan, 25-MAR-1999).

Pyriproxyfen residues were 0.07-0.16 ppm in/on 14 grapefruit samples harvested 1 day after the last of three applications at 1x. At 2x, pyriproxyfen was detected at 0.27 and 0.40 ppm in/on two treated samples.

Conclusions: The submitted field trial data on citrus fruits are adequate. Geographic representation of field trials on grapefruit, lemons, and oranges conformed to OPPTS Series 860 guidelines and an adequate number of samples were analyzed. Residues of pyriproxyfen were <0.01-0.24 ppm in/on 52 samples of oranges, lemons, and grapefruits treated at 1x. The available data support the proposed tolerance of 0.3 ppm for residues of pyriproxyfen in/on citrus fruit.

Fruiting Vegetables Group

Peppers

Valent submitted data from 10 field trials conducted in CA (4), FL (1), MI (1), NM (1), NC (1), and TX (2) during 1996 and 1997 depicting residues of pyriproxyfen in/on peppers, including three field trials with non-bell peppers (Anaheim Chile, Jalapeno M, and Big Jim) (MRID 44630107). These studies were reviewed and found to be acceptable (D253836, W. Donovan, 25-MAR-1999).

Among the 20 pepper samples harvested 14 days following 1x treatment, pyriproxyfen was nondetectable (<0.01 ppm) in/on eight, 0.01-0.06 ppm in/on 11 samples, and 0.105 ppm in/on one sample. At 2x, pyriproxyfen was detected at 0.05-0.17 ppm in/on four samples. In the two decline studies residues decreased ~50% in one study and 25% in the other from 7 days posttreatment to 28 days.

Tomatoes

Valent submitted data from 13 field trials conducted in AZ (1), CA (7), FL (2), GA (1), MI (1), and NJ (1) during 1996 and 1997 depicting residues of pyriproxyfen in/on tomatoes (MRID 44630103). These studies were reviewed and found to be acceptable (D253836, W. Donovan, 25-MAR-1999).

Among the 26 tomato samples harvested 14 days following treatment at 1x, 16 had no detectable pyriproxyfen residue (<0.01 ppm); residues in the other eight samples were 0.01-0.04 ppm. Eight samples treated at 2x bore pyriproxyfen residues of <0.01-0.11 ppm and four 5x treated samples contained 0.02-0.24 ppm.

Conclusions: The submitted field trial data on fruiting vegetables are adequate. Geographic representation of field trials on peppers and tomatoes conformed to OPPTS Series 860 guidelines and an adequate number of samples was analyzed. An adequate variety of commercially important peppers and tomatoes were included in the study. Residues of pyriproxyfen were <0.01-0.06 ppm in/on 46 samples of tomato and peppers treated at 1x; one sample bore pyriproxyfen residues at 0.105 ppm. The available data support a tolerance level of 0.20 ppm for residues of pyriproxyfen in/on fruiting vegetables.

Tree Nuts Group

The petitioner has provided data from a total of 10 field trials, 6 on almonds submitted with this petition, and 4 on walnuts that were previously reviewed, all performed in Region 10. The petitioner requests that these data be used in lieu of the required 5 almond and 5 pecan field trials specified in OPPTS GLN 860.1500.

Due to the low toxicity of pyriproxyfen (no acute dietary, cancer, or short- or intermediate-term dermal or inhalation endpoints were identified), relatively high chronic RfD (0.35 mg/kg/day), removal of the FQPA safety factor, its low use rates, and the rapid incorporation of pyriproxyfen metabolites into the general carbon pool after metabolism, HED is willing to agree to this modified data set FOR PYRIPROXYFEN ONLY. HED emphasizes that the general non-systemic nature of pyriproxyfen combined with the specific almond and walnut data showing that pyriproxyfen residues do not readily translocate from the nut shell into the nutmeat provide some confidence that finite pyriproxyfen residues should not be found in pecan nutmeat since almond shells are generally considered more porous than pecan shells (personal communication, B. Schneider, 21-APR-1999).

Almonds

Valent submitted data from six field trials conducted in CA during 1997 depicting residues of pyriproxyfen in/on almonds (MRID 44630102). These studies were reviewed and found to be acceptable (D253836, W. Donovan, 25-MAR-1999).

Residues of pyriproxyfen were non-detectable (<0.01 ppm) in/on 12 samples of nutmeat. In the studies conducted at 2x the proposed rate, residues of pyriproxyfen were <0.01 ppm in/on three samples of nutmeat, and one sample bore residues at the LOD (0.01 ppm). Residues of pyriproxyfen were 0.26-1.40 ppm in/on 12 samples of hulls. In the two trials conducted at 2x, residues of pyriproxyfen were 0.96-3.32 ppm in/on four samples of hulls.

The submitted field trial data on almonds are adequate. Residues of pyriproxyfen were non-detectable (<0.01 ppm) in/on 12 samples of nutmeat and 0.26-1.40 ppm in/on 12 samples of hulls harvested 16-21 days following the last of three foliar applications of pyriproxyfen (0.86 lb/gal) at ~0.11 lb ai/A/application (~0.33 lb ai/A/season; 1x the proposed seasonal rate). Residues of pyriproxyfen were <0.02 ppm (<LOQ) and 0.96-3.32 ppm in/on four samples each of nutmeat and hulls treated at 2x the proposed rate.

The available data support the proposed tolerance of 2.0 ppm for residues of pyriproxyfen in/on almond hulls, and the proposed tolerance of 0.02 ppm for residues of pyriproxyfen in the tree nut crop group.

Walnuts

Previously reviewed data are available from four field trials on walnuts conducted in CA during 1996 that were submitted to support a permanent tolerance petition for residues in/on walnuts (PP#7F04882, DP Barcode D238190, W. Donovan, 07-DEC-1998). Residues of

pyriproxyfen and 4'-OH-PYR were non-detectable (<0.01 ppm) in/on eight walnut samples harvested ~21 days after the last treatment.

The submitted data indicate that residues of pyriproxyfen will not exceed the proposed tolerance for walnuts (0.02 ppm) in/on samples harvested 21 days following the last of three broadcast applications of the 0.86 lb/gal EC formulation at ~50 grams ai/A/application (0.33 lb ai/A/season; 1x the maximum proposed seasonal rate). Residues of pyriproxyfen in/on eight samples of walnuts treated as described above were each less than the LOQ (<0.02 ppm).

The available walnut crop field trial data support the proposed tolerance of 0.02 ppm for residues of pyriproxyfen in/on walnuts.

Conclusions: The almond and walnut crop field trial data are adequate. HED is willing to agree to this modified data set to establish a tree nut crop group tolerance of 0.02 ppm FOR PYRIPROXYFEN ONLY.

viii. Processed Food/Feed

Oranges

In conjunction with the residue study on oranges (MRID 44630105), the petitioner submitted data depicting residues of pyriproxyfen and 4'-OH-PYR in orange commodities processed from oranges bearing measurable residues. In a field trial conducted in Manatee County, FL, pyriproxyfen (0.86 lb/gal EC) was applied three times foliarly to oranges at 100 g ai/A/application at 21-day RTIs for a total of 300 g ai/A/season (0.66 lb ai/A/season; 2x the proposed rate).

One bulk control and treated sample of oranges (440 lbs each) were harvested 1 day following the last application of pyriproxyfen. On the day of collection, the samples were shipped at ambient temperatures by overnight courier to the processing facility, Englar Food Laboratories, Moses Lake, WA where the samples were processed, within 4 days of collection, into orange fractions using simulated commercial practices, and frozen. The samples were then shipped by overnight courier (on dry ice) to the analytical laboratory, Valent Technical Center, Dublin, CA where the samples were kept at -20°C prior to analysis. The RAC samples and processed orange fractions were analyzed within 7 days of collection.

Residues of pyriproxyfen and 4'-OH-PYR were determined using method RM-33P-1-3. The validated LOQ for each analyte is 0.02 ppm in whole oranges and orange processed fractions. Concurrent method recoveries were adequate. Apparent residues of both analytes were <LOQ (<0.02 ppm) in/on duplicate control samples of each matrix with the exception of control samples of dried pulp which bore residues of 4'-OH-PYR at 0.2 ppm.

Conclusions: The submitted orange processing study is adequate and indicates that residues of pyriproxyfen do not concentrate in juice, but concentrate by 74.6x in citrus oil and 6.4x in dried pulp. Based upon these concentration factors and the HAFT residues in/on oranges of

0.22 ppm, the proposed tolerances for pyriproxyfen residues in citrus oil and in dried pulp were 20.0 and 1.5 ppm, respectively. **The citrus oil tolerance is appropriate; however, adverse effects disclosure [FIFRA §6(a)(2)] data from California indicates that a citrus dried pulp tolerance of 2.0 ppm is needed (D253882, W. Donovan, 22-MAR-1999).**

Tomatoes

Valent submitted data depicting the potential for concentration of pyriproxyfen residues in the processed commodities of tomatoes. The data were included in the submission of field trial data (MRID 44630103).

One bulk control and treated sample of tomatoes (150 lbs) were harvested 14 days following three treatments totaling 5x the maximum proposed rate from a trial conducted in CA. The samples were shipped on the day of harvest to Wm. J. Englar and Associates, Moses Lake, WA. Tomatoes were processed using simulated industrial procedures into tomato puree and paste. The samples were returned to Valent and stored at -20°C until analysis using method RM-33P-8, described above. Pyriproxyfen and PYPA were determined using the methods for tomatoes described previously.

Conclusions: This tomato processing study is adequate. Pyriproxyfen residues were 0.04 ppm in whole tomatoes, 0.02 ppm in paste, and <0.01 ppm in puree. As there was no concentration, separate tolerances for tomato paste and puree are not required.

Tree Nuts

There are no processed commodities associated with tree nuts and therefore no tolerances for processed commodities are required.

ix. Meat, Milk, Poultry, and Eggs

An adequate cattle feeding study has been previously reviewed (PP#7F04882, DP Barcode D238190, W. Donovan, 07-DEC-1998), and HED concluded that tolerances would not be required for residues of pyriproxyfen in animal commodities provided that no additional uses on livestock feed items are proposed. The maximum theoretical dietary burden (MTDB) for beef and dairy cattle was calculated at 1.69 and 1.29 ppm, respectively, using estimated tolerances for almond hulls (2.0 ppm), apple wet pomace (0.8 ppm), dried citrus pulp (1.0 ppm), cottonseed (0.05 ppm) and cotton gin byproducts (2.0 ppm).

Based on the data submitted with the current petition, the calculated MTDB (Table 3.2) for beef and dairy cattle has increased slightly to 1.91 and 1.51 ppm, respectively, based on a more appropriate tolerance of 2.0 ppm for pyriproxyfen residues in dried citrus pulp (D253882, W. Donovan, 22-MAR-1999). This adjustment does not significantly affect the maximum expected dietary burden of pyriproxyfen residues for livestock.

There are no poultry feed items associated with this petition. Therefore, no additional secondary residues are expected to occur in poultry eggs, fat, meat, and meat byproducts as a result of the proposed uses. In conjunction with the petition for use on cotton (PP#6F4737, DP Barcodes D228556, D228925, and D228926, J. Garbus, 06-MAY-1997), HED concluded that secondary residues in poultry and eggs are unlikely in light of the poultry metabolism study results.

Table 3.2. Maximum Theoretical Dietary Burdens for Beef and Dairy Cattle.

Feed Item	Tolerance (ppm)	% Dry Matter[a]	Beef Cattle		Dairy Cattle	
			% of Diet	Burden, ppm	% of Diet	Burden, ppm
Apple pomace, wet	0.8[b]	40	40	0.80	20	0.40
Cotton gin byproducts	2.0[c]	90	20	0.44	20	0.44
Citrus, pulp	2.0	91	20	0.44	20	0.44
Almond hulls	2.0	90	10	0.22	10	0.22
Cotton seed	0.05[c]	88	10	0.01	25	0.01
TOTAL			100	1.91	95	1.51

[a] From Residue Chemistry Test Guidelines (OPPTS 860.1000, Table 1).
[b] Based on apple residue data (PP#7F04882, D238190, W. Donovan, 07-DEC-1998).
[c] Based on cotton residue data (PP#6F04737, D228556, J. Garbus, 06-MAY-1997).

Conclusions: Typically, tolerances are required on all animal commodities having detectable residue levels at a 10x dosing rate or below. For the computed MTDB of 1.69 ppm in beef cattle, this would include the 3 and 9 ppm dosing levels. The only commodity having detectable pyriproxyfen residues at these levels was fat: 0.01 - 0.03 ppm. Since the MTDB calculation is based on a nutritionally unbalanced diet and includes contributions from some animal feed items that are used only regionally, HED will not require the establishment of pyriproxyfen tolerances in fat at this time. **However, should future new uses include additional animal feed items, tolerances on animal commodities will be needed.**

x. Water, Fish, and Irrigated Crops - not applicable.

xi. Food Handling Establishments - not applicable.

xii. Confined Accumulation in Rotational Crops

The Agency has determined that rotational crop studies are not required for uses of pesticides on the citrus fruits or tree nut crop groups (*OPPTS Test Guidelines, Residue Chemistry, Section 860.1850*). An adequate confined rotational crop study (MRID 44036918) was conducted in

support of the cotton petition (PP#6F4737, D228556, D228925, and D228926, J. Garbus, 06-MAY-1997). Based on a 30-day plantback interval and a treatment rate of 0.18 lb ai/A, no pyriproxyfen residues above 0.01 ppm were found in any of the following crop matrices: lettuce leaf; radish tops and roots; and wheat grain, forage, straw and chaff. Accordingly, HED concludes that a 30-day plantback interval is needed for fruiting vegetables when treated with pyriproxyfen as directed.

xiii. Field Accumulation in Rotational Crops - not applicable.

xiv. Reduction of Residues - not applicable.

xv. International Harmonization of Tolerances

There are no CODEX, Canadian, or Mexican tolerances for pyriproxyfen residues in/on citrus fruits, fruiting vegetables, or the tree nut crop groups. Therefore, international harmonization is not an issue at this time. Pyriproxyfen is scheduled as a new compound for Joint Meeting on Pesticide Residue (JMPR) review (both toxicology and residue chemistry) in 1999 (see Attachment 2).

b. Dietary Exposure (Drinking Water Source)

HED does not have monitoring data available to perform a quantitative drinking water risk assessment for pyriproxyfen at this time. However, the Environmental Fate and Effects Division (EFED) provided ground and drinking water assessments of pyriproxyfen (D. Rieder, 22-SEP-1998; D. Rieder, 13-JUL-1999). These assessments utilized the Tier 1 SCI-GROW screening model and the Tier 2 PRZM-EXAMS model to provide estimates of ground and surface water contamination from pyriproxyfen, respectively, but did not consider the behavior of degradates.

i. Ground Water

Using available fate parameters and assuming a label application rate of 3 applications at 0.11 lbs ai/acre, the estimated ground water concentration from pyriproxyfen using SCI-GROW was 0.006 ppb. These results suggest that pyriproxyfen is not likely to leach. There may be exceptional circumstances under which ground water concentration could exceed the SCI-GROW estimates. However, such exceptions should be rare since the SCI-GROW model is based exclusively on maximum ground water concentrations from studies conducted at sites and under conditions which are most likely to result in ground water contamination. The ground water concentrations generated by SCI-GROW are based on the largest 90-day average recorded during the sampling period. The concentration of 0.006 ppb can be considered as both the acute and chronic values. Pyriproxyfen is not listed in the EPA Pesticides in Ground Water Database, nor is there an EPA Maximum Contaminant Level or health advisory.

ii. Surface Water

The PRZM-EXAMS model was used to estimate surface water concentrations for pyriproxyfen resulting from its use on cotton, pome fruits & walnuts, and citrus. The maximum 1 year

average surface water concentration of pyriproxyfen was estimated at 0.106 ppb for citrus. This estimate is based on three applications of 0.09 to 0.11 lbs ai/A. The PRZM-EXAMS values represent an upper-bound estimate of the concentrations that might be found in surface water due to pyriproxyfen use.

c. Dietary Risk Assessment and Characterization

i. Chronic Risk

Dietary Exposure Evaluation Model (DEEM™) analysis for pyriproxyfen was performed in order to provide an estimate of the dietary exposure and associated risk resulting from the existing tolerances and the recommended tolerance levels for citrus fruits, fruiting vegetables (except cucurbits), and tree nuts (D257836, W. Donovan, 20-JUL-1999). The DEEM™ analysis evaluated the individual food consumption as reported by respondents in the USDA 1989-92 nationwide Continuing Surveys of Food Intake by Individuals (CSFII) and accumulated exposure to the chemical for each commodity.

The chronic Population Adjusted Dose (cPAD) is a modification of the chronic RfD to accommodate the FQPA Safety Factor. The cPAD is equal to the chronic RfD divided by the FQPA Safety Factor. Since the HED FQPA Safety Factor Committee decided to reduce the 10x safety factor to 1x (HED Doc. No. 013028, B. Tarplee, 17-DEC-1998), the cPAD is identical to the chronic RfD.

The chronic dietary exposure analysis from food sources was conducted using a chronic population adjusted dose (cPAD) of 0.35 mg/kg/day. The RfD is based on the NOAEL of 35.1 mg/kg/day in male and female rats from the Chronic Feeding/Oncogenicity study in rats (MRID 42178314), and an uncertainty factor of 100 applicable to all population subgroups.

In conducting this chronic dietary risk assessment, HED has made very conservative assumptions: 100% of all crops having pyriproxyfen tolerances will contain pyriproxyfen residues and those residues will be at the level of the established (or recommended) tolerance. Moreover, rather than making use of experimentally-determined processing factors, only DEEM™ default processing factors were used. This results in an overestimate of human dietary exposure. Thus, in making a safety determination for this tolerance, HED is taking into account this conservative exposure assessment.

DEEM™ analysis including all the appropriate pyriproxyfen tolerances results in Total Exposures that are equivalent to the following percentages of the cPAD (D257836, W. Donovan, 20-JUL-1999):

Table 3.3. Summary of Results from Chronic DEEM™ Analysis of Pyriproxyfen.

Subgroups	Total Exposure (mg/kg/day)	% cPAD
U.S. Population (48 states)	0.001411	0.4
Children (1-6 years)	0.003876	1.1
Non-hispanic other than black or white	0.001852	0.5
Hispanics	0.001592	0.5
Females (13+/nursing)	0.001660	0.5

The subgroups listed above are: (1) the U.S. population (48 states); (2) those for infants and children; and (3) the other subgroups for which the percentage of the cPAD occupied is greater than that occupied by the subgroup U.S. population (48 states).

ii. Carcinogenic Risk

The carcinogenic potential of pyriproxyfen has been evaluated by the RfD Committee (15-SEP-1995) and classified as a Group E chemical--no evidence of carcinogenicity in two acceptable animal species. Thus, a cancer risk assessment is not required.

iii. Acute Dietary Risk

No endpoint was selected by the HIARC (24-OCT-1997) for assessment of acute dietary risk. Thus no risk assessment is required.

iv. Chronic Drinking Water Risk

HED followed OPP's Interim Guidance for Conducting Drinking Water Exposure and Risk Assessments issued on 15-OCT-1998 (SOP 98.4). Thus, the PRZM/EXAMS model and the SCI-GROW model were run by the Environmental Fate and Effects Division (EFED) to produce estimates of pyriproxyfen concentrations in surface and ground water, respectively. The primary use of these models is to provide a coarse screen for sorting out pesticides for which OPP has a high degree of confidence that the true levels of the pesticide in drinking water will be less than the human health drinking water levels of comparison (DWLOCs). A human health DWLOC is the concentration of a pesticide in drinking water which would result in unacceptable aggregate risk, after having already factored in all food exposures and other non-occupational exposures for which OPP has reliable data.

$$DWLOC_{chronic} = \frac{[\text{chronic water exposure (mg/kg/day)} \times \text{(body weight)}]}{[\text{consumption (L)} \times 10^{-3}\ \text{mg}/\mu\text{g}]}$$

where chronic water exposure (mg/kg/day) = [cPAD - (chronic food + residential exposure) (mg/kg/day)]

The $DWLOC_{chronic}$ is the concentration in drinking water as part of the aggregate chronic exposure that results in a negligible cancer risk. The Agency's default body weights and consumption values used to calculate DWLOCs are as follows: 70 kg/2L (adult male), 60 kg/2L (adult female), and 10 kg/1L (child).

The results are summarized in Table 3.4 as follows:

Table 3.4. DWLOC values calculated for pyriproxyfen based on a chronic scenario.

Population Subgroup	Chronic Scenario[1]			
	cPAD mg/kg/day	DWLOC μg/L	SCI-GROW EEC in μg/L	PRZM-EXAMS[2] EEC in μg/L
U.S. Population	0.35	12,000	0.006	0.11
Children (1-6 yrs)	0.35	3,500	0.006	0.11

[1] DEEM TMRCs in mg/kg/day: U.S. Population = 0.001411, Children (1 - 6 years) = 0.003876. The average potential dose rate from residential use of pet collars is 0.00058 and 0.000081 mg/kg/day for children and U.S. population, respectively (see Table 4.1).
[2] Using the 1-year average EEC for pyriproxyfen in surface water calculated using the citrus fruit application rate.

For chronic (non-cancer) exposure to pyriproxyfen in surface and ground water, the drinking water levels of concern are 12,000 μg/L for U.S. Population and 3,500 μg/L for children (1 - 6 years). Estimated average concentrations of pyriproxyfen in surface and ground water are 0.11 ppb and 0.006 ppb, respectively. The estimated average concentrations of pyriproxyfen in surface and ground water are less than OPP's level of concern for pyriproxyfen in drinking water as a contribution to chronic aggregate exposure. Therefore, taking into account present uses and uses proposed in this action, OPP concludes with reasonable certainty that residues of pyriproxyfen in drinking water (when considered along with other sources of exposure for which OPP has reliable data) would not result in unacceptable levels of aggregate human health risk at this time.

d. Statement of the Adequacy of the Dietary Exposure Database to Assess Infants' and Children's Exposure

The dietary (food and water) exposure database for pyriproxyfen is adequate to assess infants' and children's exposure.

4. Occupational and Residential Exposure and Risk Assessment/Characterization

a. Summary of Use Patterns and Formulations

Pyriproxyfen is the active ingredient in many registered residential (indoor, non-food) products for flea and tick control. Formulations include foggers, aerosol sprays, emulsifiable concentrates, and impregnated materials (pet collars). Section 18 emergency exemptions for use in cotton, citrus and almonds have been approved. The registrant is requesting registration for use in the following crops: citrus fruits, fruiting vegetables, and tree nuts at a maximum application rate of 0.33 lb a.i. per acre per season. Both ground and aerial applications are permitted.

b. Occupational Exposure

i. Handler

There are potential short- and intermediate-term exposures to workers from the proposed uses of pyriproxyfen on citrus fruits, fruiting vegetables, and tree nuts. However, exposure and risk assessments are not warranted since toxicological endpoints of concern were not identified for short and intermediate-term exposures.

Chronic exposures are not expected from the proposed uses of pyriproxyfen, therefore a risk assessment was not conducted.

ii. Post-Application

Postapplication exposures are not of concern, based on the use pattern and the low acute toxicity of the active ingredient.

The restricted entry interval (REI) is 12 hours based on pyriproxyfen acute toxicity classification. Reentry restrictions and personal protective clothing specified on the product label should provide adequate protection from the potential postapplication exposures.

c. Residential Exposure

i. Handler

Exposure and risk assessments are not warranted since toxicological endpoints of concern were not identified for short and intermediate term exposures.

ii. Post-Application

With the exception of the pet collar uses, consumer use of pyriproxyfen typically results in short-term, intermittent exposures. Hence, chronic residential post-application exposure and risk assessments were conducted to estimate the potential risks from pet collar uses.

The risk assessment was conducted using the following assumptions: application rate of 0.58 mg ai/day (product label), average body weight for a 1 to 6 year old child of 10 kg, the active ingredient dissipates uniformly through 365 days (the label instruct to change collar once a year), 1% of the active ingredient is available for dermal and inhalation exposure per day (assumption from Draft HED Standard Operating Procedures (SOPs) for Residential Exposure Assessments, 18-DEC-1998). The assessment also assumes an absorption rate of 100%. This is a conservative assumption since the dermal absorption was estimated to be 10% (HED Hazard Identification Assessment Review Committee, 24-OCT-1997).

Table 4.1. Residential Exposure and Risk Assessment
Exposure & Risk Assessment for Homeowner Use of Pet Collars

Population Subgroup	Application Rate[1] mg/day	Average Potential Dose Rate[2] (mg/kg/day)	Chronic Term MOE[3]
Children	0.58	0.00058	61,000
Adults	0.58	0.000081	430,000

1 Product label: Reg. No. 2382-149 (0.5% pyriproxyfen, ovisterilant pet collar). Application rate = 42 gm collar x 0.5% a.i./collar x 1000 mg/1 gm x 1/365 days. Collar to be replaced once a year.

2 Potential Dose Rate (PDR) = Application rate x fraction of ai available for exposure (1%) x absorption rate(100%) x 1/(10 or 71.8 kg bw for children or adults, respectively) (Draft HED Standard Operating Procedures (SOPs) for Residential Exposure Assessments, 18-DEC-1998).

3 Dermal and Inhalation NOAEL = 35.1 mg/kg/day; MOE = NOAEL/Exposure; Adequate MOE = 100.

The estimated chronic term MOE was 61,000 for children, and 430,000 for adults. The risk estimates indicate that potential risks from pet collar uses do not exceed the Agency's level of concern.

d. Statement of the Adequacy of the Residential Exposure Database to Assess Infants' and Children's Exposure

The residential (food and water) exposure database for pyriproxyfen is adequate to assess infants' and children's exposure.

5. Aggregate Exposure and Risk Assessment Characterization

a. Acute Aggregate Exposure and Risk

An acute dietary dose and endpoint was not identified. Thus the risk from acute aggregate exposure is considered to be negligible.

b. Short- and Intermediate-term Aggregate Exposure and Risk

No short- or intermediate-term residential exposure assessment is required for pyriproxyfen since the HED HIARC determined (J. Rowland, 24-OCT-1997) that short-term and intermediate-term dermal and inhalation risk assessments for occupational and residential exposure are not required (due to the lack of significant toxicological effects observed, see previous toxicological discussion).

c. Chronic Aggregate Exposure and Risk

Using the conservative exposure assumptions described above, HED has calculated that the maximum percentage of the cPAD that will be utilized by dietary (food) exposure to residues of pyriproxyfen is **1.1** percent for children (1 - 6 years). Chronic residential exposure to pyriproxyfen from pet collars is estimated to increase total pyriproxyfen exposure of infants and children only marginally (see Table 4.1). Despite the potential for exposure to pyriproxyfen in drinking water, HED does not expect the aggregate exposure to exceed 100% of the cPAD.

HED bases this determination on a comparison of estimated concentrations of pyriproxyfen in surface and ground water to levels of concern for pyriproxyfen in drinking water. The estimates of pyriproxyfen in surface and ground water are derived from water quality models that use conservative assumptions regarding the pesticide transport from the point of application to surface and ground water. Because HED considers the aggregate risk resulting from multiple exposure pathways associated with the pesticide's uses, levels of concern in drinking water may vary as those uses change. If new uses are added in the future, HED will reassess the potential impact of pyriproxyfen in food and drinking water as part of the aggregate chronic risk assessment process.

Taking into account the completeness and reliability of the toxicity data and this conservative exposure assessment, HED concludes that there is a reasonable certainty that no harm will result to infants and children from chronic aggregate exposure to pyriproxyfen residues.

6. Other Food Quality Protection Act Considerations

a. Cumulative Risk from Exposure to Substances with a Common Mechanism of Toxicity

Pyriproxyfen is a member of the phenyl ether insect growth regulator class of chemicals. It contains the diphenyl ether moiety that is also found in several herbicides which, unlike pyriproxyfen, also contain halogens.

Section 408(b)(2)(D)(v) of the Food Quality Protection Act requires that, when considering whether to establish, modify, or revoke a tolerance, the Agency consider "available information" concerning the cumulative effects of a particular pesticide's residues and "other substances that have a common mechanism of toxicity." The Agency believes that "available information" in this context might include not only toxicity, chemistry, and exposure data, but also scientific policies and methodologies for understanding common mechanisms of toxicity and conducting cumulative risk assessments. For most pesticides, although the Agency has some information in its files that may turn out to be helpful in eventually determining whether a pesticide shares a common mechanism of toxicity with any other substances, EPA does not at this time have the methodologies to resolve the complex scientific issues concerning common mechanism of toxicity in a meaningful way. EPA has begun a pilot process to study this issue further through the examination of particular classes of pesticides. The Agency hopes that the results of this pilot process will increase the Agency's scientific understanding of this question such that EPA will be able to develop and apply scientific principles for better determining which chemicals have a common mechanism of toxicity and evaluating the cumulative effects of such chemicals. The Agency anticipates, however, that even as its understanding of the science of common mechanisms increases, decisions on specific classes of chemicals will be heavily dependent on chemical specific data, much of which may not be presently available.

Although at present the Agency does not know how to apply the information in its files concerning common mechanism issues to most risk assessments, there are pesticides for which the common mechanism issues can be resolved. These pesticides include pesticides that are toxicologically dissimilar to existing chemical substances (in which case the Agency can conclude that it is unlikely that a pesticide shares a common mechanism of activity with other substances) and pesticides that produce a common toxic metabolite (in which case common mechanism of activity will be assumed).

EPA does not have, at this time, available data to determine whether pyriproxyfen has a common mechanism of toxicity with other substances or how to include this pesticide in a cumulative risk assessment. For the purposes of these tolerance actions, therefore, EPA has not assumed that pyriproxyfen has a common mechanism of toxicity with other substances.

b. Endocrine Disrupter Effects

EPA is required to develop a screening program to determine whether certain substances (including all pesticides and inerts) "may have an effect in humans that is similar to an effect produced by a naturally occurring estrogen, or such other endocrine effect...." The Agency is

currently working with interested stakeholders, including other government agencies, public interest groups, industry and research scientists in developing a screening and testing program and a priority setting scheme to implement this program. Congress has allowed 3 years from the passage of FQPA (August 3, 1999) to implement this program. At that time, EPA may require further testing of this active ingredient and end use products for endocrine disrupter effects.

c. Determination of Safety (U.S. Population, Infants, and Children)

Using the exposure assumptions described in this document, HED concludes that the percentage of the cPAD that will be utilized by chronic dietary (food only) exposure to residues of pyriproxyfen is less than 1.1% of the cPAD. The estimated chronic-term margin of exposure (MOE) from homeowner use of pet collars was 61,000 for children and 430,000 for adults, well below the Agency's level of concern. Despite the potential for exposure to pyriproxyfen in drinking water, HED does not expect the chronic risk to exceed HED's level of concern. HED concludes there is a reasonable certainty that no harm will result to the US Population, Infants, or Children from chronic aggregate exposure to pyriproxyfen residues.

IV. DATA REQUIREMENTS

a. Toxicology - None.

b. Chemistry

Revised KNACK™ and ESTEEM™ labels with specification of ground or aerial application equipment and amount of spray volume clearly indicated under Special Instructions for each pest use for almonds, citrus, and walnuts are needed. Also, the labels should be amended to specify a minimum RTI for each crop matching what was used in the crop field trials. Finally, a 30-day plantback interval for rotational crops should be added to the fruiting vegetable labels.

c. Occupational/Residential - None.

V. REFERENCES

DP Barcode:	D228556, D228925, and D228926
Subject:	PP#6F4737. Pyriproxyfen on Cotton. Evaluation of Analytical Methods, Field Trial, and Processing Residue Data.
From:	J. Garbus
To:	K. Boyle
Dated:	06-MAY-1997
MRID(s):	44036901-44036904, 44036918-44036920, 44036922-44036930, 44037201, and 4437204.

DP Barcode:	None
Subject:	Pyriproxyfen: Report of the Hazard Identification Assessment Review Committee.
From:	J. Rowland
To:	R. Loranger
Dated:	24-OCT-1997

DP Barcode:	D241303, D228499
Subject:	PP#6F04737. Pyriproxyfen on cotton. HED Risk Assessment.
From:	W. Donovan, W. Dykstra, B. Tarplee
To:	S. Lewis, J. Tavano
Dated:	27-FEB-1998

DP Barcode:	D243702
Subject:	ID#98CA0011. Section 18 Exemption for the use of Pyriproxyfen on Citrus in California.
From:	M. Lamont, W. Dykstra, B. Tarplee
To:	A. Beard, R. Forrest
Dated:	25-MAR-1998

DP Barcode:	D249443
Subject:	Review of Environmental Risk from using Pyriproxyfen to Control Fire Ants in Almonds in California and Drinking Water Assessment.
From:	D. Rieder
To:	A. Beard
Dated:	22-SEP-1998
DP Barcode:	D249441

Subject:	ID#98CA0041. Section 18 Exemption for the use of Pyriproxyfen on Almonds to Combat Fire Ants in California.
From:	W. Donovan, W. Dykstra, M. Christian
To:	A. Beard, R. Forrest
Dated:	26-OCT-1998

DP Barcode:	D250953
Subject:	Pyriproxyfen. Results of the Metabolism Assessment Review Committee Meeting Held on 10-NOV-1998.
From:	W. Donovan, W. Dykstra
To:	G. Kramer
Dated:	19-NOV-1998

DP Barcode:	D238190
Subject:	Pyriproxyfen in/on Pome Fruits. Evaluation of Reside Data and Analytical Methods.
From:	W. Donovan
To:	S. Lewis and J. Tavano
Dated:	04-DEC-1998

DP Barcode:	D252371
Subject:	PP#s 7F04882 and 8F05022. Pyriproxyfen in/on Citrus Fruits, Pome Fruits, Fruiting Vegetables, and Tree Nuts. Request for Petition Method Validation (PMV).
From:	W. Donovan
To:	D. Marlow
Dated:	28-JAN-1999

DP Barcode:	D253882
Subject:	Pyriproxyfen in/on Citrus Pulp, Dried. Review of Temporary Tolerance Level Based on Datat Submitted Under FIFRA 6(a)(2).
From:	W. Donovan
To:	A. Beard, R. Forrest
Dated:	22-MAR-1999

DP Barcode:	D253836
Subject:	Pyriproxyfen in/on Citrus, Fruiting Vegetables, and Tree Nuts. Evaluation of Residue Data and Analytical Methods.
From:	W. Donovan
To:	S. Lewis, J. Tavano
Dated:	25-MAR-1999
DP Barcode:	None
Subject:	PP#s 7F04882 and 8F05022. Pyriproxyfen in/on Citrus Fruits, Fruiting Vegetables, and Tree Nuts. Validation of the Residue Analytical Methods for Tolerance Enforcement
From:	A.J. Krynitsky, D.M. Swineford
To:	K. Whitby, A. Layne
Dated:	21-JUN-1999
DP Barcode:	D257337
Subject:	PP#s 7F04882 and 8F05022. Pyriproxyfen in/on Citrus Fruits, Fruiting Vegetables, and Tree Nuts. Results of Petition Method Validation (PMV) Request.
From:	W. Donovan
To:	A. Layne, J. Tavano
Dated:	01-JUL-1999
DP Barcode:	D249530 and D249524
Subject:	EFED Risk Assessment and Drinking Water Assessment for Proposal to use Pyriproxyfen on Citrus, Almonds, and Fruiting Vegetables.
From:	D. Rieder
To:	A. Layne
Dated:	13-JUL-1999
DP Barcode:	D257836
Subject:	Pyriproxyfen - Chronic Dietary Exposure Analysis.
From:	W. Donovan
To:	W. Dykstra
Dated:	21-JUL-1999

ATTACHMENTS:

Attachment 1: Chronic DEEM Run: W. Donovan, 21-JUL-1999
Attachment 2: International Residue Limit (Codex) Status Sheet
Attachment 3: Pyriproxyfen drinking water assessment: D. Rieder, 13-JUL-1999.
Attachment 4: Pyriproxyfen - Report of the Hazard Identification Assessment Review Committee: J. Rowland, 24-OCT-1997.

cc with attachments: W. Donovan
cc without attachments: W. Dykstra, M. Christian, O. Odiott, RAB1 File
RDI: RAB1 Chemists (15-JUL-1999), M. Morrow (22-JUL-1999)
W.H. Donovan: 806T: CM#2: (703)-305-7330: 02-AUG-1999

Attachment 1

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF
PREVENTION, PESTICIDES, AND
TOXIC SUBSTANCES

MEMORANDUM

DATE: 21-JUL-1999

SUBJECT: Pyriproxyfen - Chronic Dietary Exposure Analysis. Chemical#: 129032. Caswell#: 954. DP Barcode: D257836.

FROM: William H. Donovan, Ph.D., Chemist
RAB1/HED (7509C)

THROUGH: David Hrdy, Biologist
Carol Christensen, EPS
Dietary Exposure Science Advisory Council Reviewers

Melba Morrow, D.V.M., Branch Senior Scientist
RAB1/HED (7509C)

TO: William Dykstra, Ph.D., Toxicologist
RAB1/HED (7509C)

Action Requested

Provide an estimate of the chronic dietary exposure and associated risk for pyriproxyfen resulting from existing permanent and temporary tolerances, and proposed permanent tolerances for citrus fruits, fruiting vegetables (except cucurbits), and tree nuts submitted in support of PP#8F05022.

The recommended tolerance levels for PP#8F05022 are as follows:

Citrus Fruits:	0.3 ppm
Fruiting Vegetables:	0.2 ppm
Tree Nuts:	0.02 ppm

A previous chronic dietary exposure analysis incorporating all available tolerances using the DEEM™ system was completed on 16-FEB-1999 (W. Donovan). The present run makes use of a tolerance level of 0.2 instead of 0.1 ppm for the fruiting vegetables crop group and makes use of DEEM™ default values instead of experimentally-determined processing factors.

Toxicological Endpoints

Chronic RfD
The chronic Reference Dose (RfD) for regulatory purposes is 0.35 mg/kg/day. The Hazard Identification Assessment Review Committee (HIARC) selected a NOAEL of 35.1 mg/kg/day based on 2-year and 90-day feeding studies in rats and an uncertainty factor of 100. The LOAEL of 141 mg/kg/day was based on a 17% decreased body weight gain in treated female rats compared to controls (Memo, J. Rowland, 24-OCT-1997). The HIARC also determined that the 10 x factor to account for enhanced sensitivity of infants and children (as required by FQPA) should be removed. The rationale presented was as follows:
(1) Developmental toxicity studies showed no increased sensitivity in fetuses as compared to maternal animals following *in utero* exposures in rats and rabbits.
(2) A two generation reproduction toxicity study in rats showed no increased sensitivity in pups as compared to adults.
(3) The toxicology data base is complete and there are no data gaps.

Acute RfD
No acute dietary reference dose was selected for pyriproxyfen because there were no effects observed in oral toxicology studies including the developmental toxicity studies in rats or rabbits that could be attributable to a single dose (exposure) (Memo, J. Rowland, 24-OCT-1997). Thus, no acute dietary exposure analysis is needed for pyriproxyfen.

FQPA Recommendation
In a 07-DEC-1998 meeting of the HED FQPA Safety Factor Committee, the HIARC decision to remove the 10x factor was confirmed (HED Doc. No. 013028, B. Tarplee, 17-DEC-1998). The chronic Population Adjusted Dose (cPAD) is a modification of the chronic RfD to accommodate the FQPA safety factor. The cPAD is equal to the chronic RfD divided by the FQPA safety factor. Since the HED FQPA Safety Factor Committee determined to remove the 10X Safety Factor, the chronic RfD is identical to the cPAD.

Cancer
Pyriproxyfen is classified as Category E: not carcinogenic in two acceptable animal studies (PP#6F04737, D241303 & D228499, W. Donovan, W. Dykstra, B. Tarplee, 27-FEB-1998).

Residue Information

A permanent tolerance for pyriproxyfen residues in/on cotton seed has been established (PP6F04737) and is listed under 40 CFR §180.534. There are pending permanent tolerances for pyriproxyfen use on pome fruits and walnuts at 0.2 and 0.02 ppm, respectively. Several time-limited tolerances (TLT) have been established in conjunction with Section 18 actions (98CA0011, 98OR0013, and 98FL0005). These tolerances are listed under 40 CFR § 180.510 with an expiration date of 31-JUL-1999.

The current Section 3 proposal for pyriproxyfen tolerances of 0.3, 0.2, and 0.02 ppm on citrus fruits, fruiting vegetables (except cucurbits), and tree nuts, respectively, was based on crop field

trial data. The present analysis was made using tolerance-level residues and a 100% crop treated assumption in conjunction with the DEEM™ default processing factors (Tier 1 approach).

Results

Chronic Analysis

The Dietary Exposure Evaluation Model (DEEM™) analysis evaluated the individual food consumption as reported by respondents in the USDA 1989-92 nationwide Continuing Surveys for Food Intake by Individuals (CSFII) and accumulated exposure to the chemical for each commodity. Since the FQPA safety factor has been removed for all population subgroups, HED's level of concern is 100% cPAD. The chronic DEEM™ analysis used mean consumption (3 day average) data and gave the results listed in Table 1:

Table 1. Summary of Results from Chronic DEEM™ Analysis of Pyriproxyfen.

Subgroups	Exposure (mg/kg/day)	% cPAD
U.S. Population (48 states)	0.001411	0.4
Children (1-6 years)	0.003876	1.1
Non-hispanic other than black or white	0.001852	0.5
Hispanics	0.001592	0.5
Females (13+/nursing)	0.001660	0.5

The population subgroups listed include 1) the U.S. Population (48 states), 2) the most highly exposed subgroup from the infant and children subgroups and 3) other subgroups with exposures higher than that of the U.S. Population (48 states).

Conclusion

The results of this analysis indicate that the chronic dietary risk associated with existing uses and the proposed use of pyriproxyfen is below the Agency's level of concern (100% cPAD). The present analysis represents a highly-conservative estimation of risk from pyriproxyfen since no data refinement was performed.

Attachment 1: Pyriproxyfen Tier 1 residue file for chronic DEEM™ analysis.
Attachment 2: Pyriproxyfen Chronic DEEM™ analysis.

cc: W. Donovan (RAB1); M. Sahafeyen (CEB1)
RDI: D. Hrdy (19-JUL-1999), C. Christensen (20-JUL-1999)
W. Donovan:CM#2: 804-K:(703)305-7330:21-JUL-1999

Attachment 1. Pyriproxyfen Tier 1 residue file for chronic DEEM™ analysis.

Filename: C:\deemepa\129032.r96Chemical name: Pyriproxyfen
RfD(Chronic): .35 mg/kg bw/day NOEL(Chronic): 35.1 mg/kg bw/day
RfD(Acute): 0 mg/kg bw/day NOEL(Acute): 0 mg/kg bw/day
Date created/last modified: 07-19-1999/07:29:40/8 Program ver. 6.77

Food Code	Crop Grp	Food Name	RESIDUE (ppm)	RDF #	Adj.Factors #1	#2	Comment
20	10	Citrus citron	0.300000	0	1.000	1.000	N 8F05022
22	10	Grapefruit-peeled fruit	0.300000	0	1.000	1.000	N 8F05022
23	10	Grapefruit-juice	0.300000	0	2.100	1.000	N 8F05022
24	10	Kumquats	0.300000	0	1.000	1.000	N 8F05022
26	10	Lemons-peeled fruit	0.300000	0	1.000	1.000	N 8F05022
27	10	Lemons-peel	0.300000	0	1.000	1.000	N 8F05022
28	10	Lemons-juice	0.300000	0	2.000	1.000	N 8F05022
30	10	Limes-peeled fruit	0.300000	0	1.000	1.000	N 8F05022
31	10	Limes-peel	0.300000	0	1.000	1.000	N 8F05022
32	10	Limes-juice	0.300000	0	2.000	1.000	N 8F05022
33	10	Oranges-juice-concentrate	0.300000	0	6.700	1.000	N 8F05022
34	10	Oranges-peeled fruit	0.300000	0	1.000	1.000	N 8F05022
35	10	Oranges-peel	0.300000	0	1.000	1.000	N 8F05022
36	10	Oranges-juice	0.300000	0	1.800	1.000	N 8F05022
37	10	Tangelos	0.300000	0	1.000	1.000	N 8F05022
38	10	Tangerines	0.300000	0	1.000	1.000	N 8F05022
39	10	Tangerines-juice	0.300000	0	2.300	1.000	N 8F05022
40	14	Almonds	0.020000	0	1.000	1.000	N 8F05022
41	14	Brazil nuts	0.020000	0	1.000	1.000	N 8F05022
42	14	Cashews	0.020000	0	1.000	1.000	N 8F05022
43	14	Chestnuts	0.020000	0	1.000	1.000	N 8F05022
44	14	Filberts (hazelnuts)	0.020000	0	1.000	1.000	N 8F05022
45	14	Hickory nuts	0.020000	0	1.000	1.000	N 8F05022
46	14	Macadamia nuts (bush nuts)	0.020000	0	1.000	1.000	N 8F05022
47	14	Pecans	0.020000	0	1.000	1.000	N 8F05022
48	14	Walnuts	0.020000	0	1.000	1.000	N 8F05022
49	14	Butter nuts	0.020000	0	1.000	1.000	N 8F05022
50	0	Pistachio nuts	0.020000	0	1.000	1.000	N 8F05022
51	14	Beech-nuts	0.020000	0	1.000	1.000	N 8F05022
52	11	Apples	0.200000	0	1.000	1.000	7F04882
53	11	Apples-dried	0.200000	0	8.000	1.000	7F04882
54	11	Apples-juice/cider	0.200000	0	1.300	1.000	7F04882
55	11	Crabapples	0.200000	0	1.000	1.000	7F04882
56	11	Pears	0.200000	0	1.000	1.000	7F04882
57	11	Pears-dried	0.200000	0	6.250	1.000	7F04882
58	11	Quinces	0.200000	0	1.000	1.000	7F04882
64	12	Nectarines	0.100000	0	1.000	1.000	7F04882
65	12	Peaches	0.100000	0	1.000	1.000	7F04882
66	12	Peaches-dried	0.100000	0	7.000	1.000	7F04882
67	12	Plums (damsons)	0.100000	0	1.000	1.000	7F04882
68	12	Plums-prunes (dried)	0.100000	0	5.000	1.000	7F04882
69	12	Plums/prune-juice	0.100000	0	1.400	1.000	7F04882
81	11	Loquats	0.200000	0	1.000	1.000	7F04882
139	8	Paprika	0.200000	0	1.000	1.000	N 8F05022
154	8	Eggplant	0.200000	0	1.000	1.000	N 8F05022
155	8	Peppers-sweet(garden)	0.200000	0	1.000	1.000	N 8F05022
156	8	Peppers-chilli incl jalapeno	0.200000	0	1.000	1.000	N 8F05022
157	8	Peppers-other	0.200000	0	1.000	1.000	N 8F05022
158	8	Pimientos	0.200000	0	1.000	1.000	N 8F05022
159	8	Tomatoes-whole	0.200000	0	1.000	1.000	N 8F05022
160	8	Tomatoes-juice	0.200000	0	1.500	1.000	N 8F05022
161	8	Tomatoes-puree	0.200000	0	3.300	1.000	N 8F05022
162	8	Tomatoes-paste	0.200000	0	5.400	1.000	N 8F05022
163	8	Tomatoes-catsup	0.200000	0	2.500	1.000	N 8F05022
290	0	Cottonseed-oil	0.050000	0	1.000	1.000	6F04737
291	0	Cottonseed-meal	0.050000	0	1.000	1.000	6F04737

377	11	Apples-juice-concentrate	0.200000	0	3.900	1.000	7F04882
404	11	Pears-juice	0.200000	0	1.000	1.000	7F04882
420	10	Tangerines-juice-concentrate	0.300000	0	7.350	1.000	7F04882
423	8	Tomatoes-dried	0.200000	0	14.300	1.000	N 8F05022
431	14	Walnut oil	0.020000	0	1.000	1.000	7F04882
441	10	Grapefruit-juice-concentrate	0.300000	0	8.260	1.000	N 8F05022
442	10	Lemons-juice-concentrate	0.300000	0	11.400	1.000	N 8F05022
443	10	Limes-juice-concentrate	0.300000	0	6.000	1.000	N 8F05022
448	10	Grapefruit peel	0.300000	0	1.000	1.000	N 8F05022
497	98	Balsam pear	0.200000	0	1.000	1.000	7F04882

Attachment 2: Pyriproxyfen Chronic DEEM™ analysis

U.S. Environmental Protection Agency Ver. 6.76
DEEM Chronic analysis for PYRIPROXYFEN (1989-92 data)
Residue file name: C:\deemepa\129032.r96 Adjustment factor #2 NOT used.
Analysis Date 07-19-1999/08:02:03 Residue file dated: 07-19-1999/08:00:00/8
Reference dose (RfD, CHRONIC) = .35 mg/kg bw/day
COMMENT 1: 8F05022 Citrus, Fruiting Vegetables, Tree Nuts

Total exposure by population subgroup

Population Subgroup	Total Exposure mg/kg body wt/day	Total Exposure Percent of Rfd
U.S. Population (total)	0.001411	0.4%
U.S. Population (spring season)	0.001324	0.4%
U.S. Population (summer season)	0.001371	0.4%
U.S. Population (autumn season)	0.001498	0.4%
U.S. Population (winter season)	0.001445	0.4%
Northeast region	0.001613	0.5%
Midwest region	0.001312	0.4%
Southern region	0.001275	0.4%
Western region	0.001555	0.4%
Hispanics	0.001592	0.5%
Non-hispanic whites	0.001377	0.4%
Non-hispanic blacks	0.001408	0.4%
Non-hisp/non-white/non-black)	0.001852	0.5%
All infants (< 1 year)	0.002439	0.7%
Nursing infants	0.001610	0.5%
Non-nursing infants	0.002788	0.8%
Children 1-6 yrs	0.003876	1.1%
Children 7-12 yrs	0.002244	0.6%
Females 13-19(not preg or nursing)	0.001278	0.4%
Females 20+ (not preg or nursing)	0.000968	0.3%
Females 13-50 yrs	0.001046	0.3%
Females 13+ (preg/not nursing)	0.001250	0.4%
Females 13+ (nursing)	0.001660	0.5%
Males 13-19 yrs	0.001268	0.4%
Males 20+ yrs	0.000939	0.3%
Seniors 55+	0.000995	0.3%
Pacific Region	0.001573	0.4%

Attachment 2

INTERNATIONAL RESIDUE LIMIT STATUS

Chemical Name:	Common Name: pyriproxyfen	X□ Proposed tolerance □ Reevaluated tolerance □ Other	Date: 02-AUG-1999

Codex Status (Maximum Residue Limits)	U. S. Tolerances
X□ No Codex proposal step 6 or above □ No Codex proposal step 6 or above for the crops requested	Petition Number: 8F05022 DP Barcode: D249526 Other Identifier:
Residue definition (step 8/CXL): N/A	Reviewer/Branch: W. Donovan/RAB1
	Residue definition: pyriproxyfen

Crop (s)	MRL (mg/kg)	Crop(s)	Tolerance (ppm)
		Citrus fruits	0.3 ppm
		Fruiting Vegetables	0.2 ppm
		Tree Nuts	0.02 ppm
		Almond, hulls	2.0 ppm
		Citrus, oil	20.0 ppm
		Citrus, pulp, dried	2.0 ppm

Limits for Canada	Limits for Mexico
X□ No Limits □ No Limits for the crops requested	X□ No Limits □ No Limits for the crops requested
Residue definition: N/A	Residue definition: N/A

Crop(s)	MRL (mg/kg)	Crop(s)	MRL (mg/kg)

Notes/Special Instructions: Codex, Scheduled as a new chemical in 1999 (tox and residue)

Rev 1998

Attachment 3

013668

NEW USE REVIEW

Subject: EFED Risk Assessment and Drinking Water Assessment for Proposal to use Pyriproxyfen on Citrus, Almonds and Fruiting Vegetables (Tomatoes and Peppers); D249530 and D249524; PC Code 129032

From: Daniel Rieder, Chief 7/13/99
Environmental Risk Branch III, EFED

To: Arnold Layne, Chief
Insecticide Branch, RD

Executive Summary:

The EFED is presenting the assessment results for the proposal to add citrus, almonds and fruiting vegetables (tomatoes and peppers) to the Pyriproxyfen label. Based on this analysis, the use of pyriproxyfen on these new sites represents a chronic risk (but not acute risk) to freshwater aquatic invertebrates, but is not expected to be a risk to other organisms. Pyriproxyfen is degraded by photolysis and metabolic processes and has low mobility. It is unlikely to reach ground water in appreciable quantities. It may reach surface waters by drift or soil runoff, however it is expected to partition into sediment. Available ecological effects and environmental fate data are generally adequate to assess pyriproxyfen for these uses. See the Data Adequacy section for further discussion of data gaps and uncertainties. For further information, please see the March 27, 1998 review D228489.

Proposed Uses

Table showing the new proposed use patterns for pyriproxyfen

Use Site	Appl Rate	Number appls per year and maximum amount to be applied	Comments on use pattern
Almonds	10-17 fl oz per acre 0.06 - 0.11 lb ai/acre	up to 3 per season (season max = 49 oz)	spray blast assumed

Citrus	17 fl oz per acre 0.11 lb ai/acre	up to 3 per season (season max=49 oz)	spray blast assumed
Vegetables (pepper and tomato)	6-10 fl oz per acre 0.04-0.067 lb ai/acre	up to 2 per season (season max=20 oz)	ground only

Previously, EFED had evaluated pyriproxyfen for use on cotton, walnuts, apples and pears. In the previous review, for cotton, it was assumed only one application of 0.054 to 0.067 lbs ai/A. Three applications of 0.09 to 0.11 lbs ai/A were assessed for apples, pears and walnuts.

Since these new uses have rates and patterns similar to previously reviewed uses, the exposure and risks are considered to be similar. For comparison purposes, the walnut and pome fruit (apples and pears) rates equal the proposed citrus and almonds rates. Even though the rates are the same, the aquatic exposure from citrus use was modeled for this review using PRZM EXAMS because citrus sites sometimes result in higher aquatic EECs than these other sites. The cotton rate for a single application equals the proposed tomatoes and peppers rates but tomatoes and peppers may be treated twice, compared to a single application for cotton.

The fact that cotton is only treated once, and peppers and tomatoes are proposed for two treatments per season is not consequential to the conclusions. For **drinking water**, the use rate on citrus, walnuts, almonds and pome fruits is higher, and has 3 applications per year, so these will determine the drinking water screening level EEC. For **ecological risk**, there is a wide margin of safety (i.e. minimal risk) for all organisms except for aquatic invertebrates. And all previously reviewed uses (including cotton with a single application) resulted in high chronic risk to aquatic invertebrates, so peppers and tomatoes, with two applications, would also be considered a high chronic risk to these organisms.

Environmental Fate Summary:

Extracted from the March 27, 1998 review D228489.

Pyriproxyfen has low volatility, low water solubility and is stable to hydrolysis. When exposed to light, pyriproxyfen is not very persistent with photolysis half-lives of 3.7 - 6.4 days in water and 6.8 - 8.5 days in soil. An acceptable field dissipation study from California resulted in a half-life of 36 days. Field dissipation half-lives from supplemental studies in Mississippi and California are 3.5 and 15.6 days, respectively. Aerobic soil metabolism half-lives range from 6.4 to 9 days. It is somewhat more persistent under aerobic aquatic conditions with aquatic aerobic metabolism half-lives of 16 to 21 days. Under **anaerobic** conditions, pyriproxyfen is substantially more persistent. Data from a supplemental anaerobic aquatic study indicated that the calculated t-1/2 was ~750 days in flooded sediment.

The sediment/water partitioning of pyriproxyfen (Freundlich adsorption K_{fads} = 11.7, $1/n_{ads}$ = 1.03) indicates that there will be some partitioning into suspended and bottom sediment. Pyriproxyfen

has low mobility. However, Kfads of one degradate, 4'-OH pyriproxyfen, indicates potentially slight mobility. The other degradate, PYPAC, is mobile.

Pyriproxyfen shows moderate bioconcentration in fish (465 to 2,390 X). The depuration rate is rapid.

Estimated Drinking Water Concentrations

Pyriproxyfen can contaminate surface water through spray drift and/or soil runoff. The PRZM/EXAMS tier II drinking water model assumed 5% spray drift, and the model indicated that the spray drift component contributed the most to the annual drinking water EEC. Based on information from environmental fate studies, parent pyriproxyfen is not likely to leach to ground-water in appreciable quantities.

The modeling done for cotton in the D228489 March 27, 1998 review is applicable to these new proposed vegetable uses (peppers and tomatoes). Please see table below.

Even though citrus has the same application rates as walnuts and pome fruits that were modeled for the previous review (D228489), PRZM-EXAMS was rerun using a Florida citrus scenario. The results of that modeling run are included as attachment 1, and summarized in the table below.

	Aquatic EECs (parts per billion)					
Crop	Peak	96 Hrs	21 Days	60 Days	90 Days	1 Year
From March 27, 1998 D228489 review						
Cotton	0.216	0.147	0.078	0.054	0.048	0.034
Apples, Pears & Walnuts	0.677	0.448	0.197	0.142	0.141	0.103
New modeling for D249530 and D249524						
Citrus	0.456	0.324	0.217	0.174	0.154	0.106

As can be seen, the EECs from citrus are not significantly different than those for apples, pears and walnuts. This is because pyriproxyfen binds tightly, and most of the residue estimation in surface water was due to drift, not runoff, and current models assumes drift is the same for spray blast, regardless of whether it is citrus, walnuts, almonds or pome fruits.

Drinking Water Summary

EFED modeled pyriproxyfen concentrations in surface water and ground water sources of drinking water for cotton (representing peppers and tomatoes), walnuts (representing almonds) and citrus (new modeling). For surface water, the PRZM-EXAMS model estimated 60-day average concentrations are 0.054 ug/L for peppers and tomatoes, 0.142 ug/L for almonds, and 0.174 ug/L for citrus. For ground water, the SCI-GROW model resulted in a default value of 0.006 ug/L for all uses.

Degradates were not modeled due to lack of data.

Ecological Toxicity:

Extracted from the March 27, 1998 review D228489. For detailed toxicity data, please see the previous review

Toxicity of Technical Pyriproxyfen

Surrogate Species and Test Type	Toxicity
Rat acute oral	LD50=4400 mg/kg
Rat 2-generation reproduction	NOEL=1000 ppm
Bird acute oral (mallard and bobwhite)	LD50>2000 mg/kg
Bird subacute dietary (mallard and bobwhite)	LC50>5200 ppm
Bird reproduction (mallard and bobwhite)	NOEL=600 ppm
Honey bee acute contact	LD50>100 ug/bee
Fish 96-hour acute (bluegill and rainbow trout)	LC50>270 ppm LC50>325 ppm
Daphnia magna 48-hour acute	EC50=400 ppb
Fish early life stage (rainbow trout)	NOAEC = 4.3 ppb
Daphnia 21-day life cycle	NOAEC = 0.015 ppb
Estuarine fish 96-hour acute (sheepshead minnow)	LC50>320 ppb
Estuarine Invertebreate 96-hour acute (Mysid shrimp)	EC50=67 ppb (supplemental study)
Mysid reproduction test	NOAEC≤0.81 ppb (supplemental study)
Aquatic plant acute (duckweed and algae)	EC50>180 ppb EC50≤56 ppb

Toxicity of a formulation containing 10% Pyriproxyfen

Species	Toxicity
rainbow trout 96-hour acute	LC50=450 ppb measured pyriproxyfen

bluegill sunfish 96-hour acute LC50=590 ppb measured pyriproxyfen

Pyriproxyfen is practically non-toxic to birds and mammals. While a contact study suggests that pyriproxyfen is practically non-toxic to honey bees, the study has tested a life-stage which would be insensitive based on the mode of action of pyriproxyfen. Pyriproxyfen is very highly toxic to mysid shrimp and highly toxic to aquatic invertebrates and green algae and, as a 10 percent ai formulation, to freshwater fish. Determination of other acute aquatic toxicity values are affected by the limited water solubility of pyriproxyfen (0.367 mg/L). Reproduction is affected at low ppb levels for fish and mysids and in pptr for daphnids.

Ecological Risk

Overall, the proposed pyriproxyfen uses on almonds, citrus, peppers and tomatoes are not expected to cause direct, adverse effects on mammals, birds, and freshwater and estuarine fish. However, aquatic invertebates are expected to be at risk of chronic effects from these uses.

Risk to Birds and Mammals

Following an application of pyriproxyfen at 0.11 lb ai/acre (citrus and almonds), exposure on avian and mammal food items is not expected to exceed approximately 26 ppm (short grass). With multiple applications (3), the residues might be higher, but the concentrations are still expected to be significantly lower than the dietary concentrations that did not result in mortality to birds (LC50>5200 ppm in subacute testing) or sublethal effects (NOAEL=600 ppm in reproduction testing) and mortality or sublethal effects in rats (NOAEL=1000 ppm, rat reproduction study). This indicates a low potential for either acute or chronic risk to birds or mammals.

Risk to Fish and Invertebrates

Table presenting acute and chronic risk quotients for aquatic invertebrates (as represented by Daphnia magna, 48-hour EC50 = 400 ppb and 21-day reproductive NOAEC=0.015 ppb)

Crop	EEC (ppb)	Acute Risk Quotients	Chronic Risk Quotients
Peppers, Tomatoes (single application at 0.067 lb ai/a)	peak 0.21 ---------- 21-day 0.078 ----------	**<0.01** ----------	**5.2**
Citrus (3 applications at 0.11 lb ai/a)	peak 0.46 ---------- 21-day 0.20 ----------	**<0.01** ----------	**13**
Almonds (3 applications at 0.11 lb ai/a)	peak 0.67 ---------- 21-day 0.21 ----------	**<0.01** ----------	**14**

This table shows the acute and chronic risk quotients for aquatic invertebrates, indicating chronic risk to invertebrates but not acute risk.

See attachment 2 for a discussion of the potential risks to aquatic invertebrates.

These aquatic EECs are substantially lower than the rainbow trout LC50 of 450 ppb (measured pyriproxyfen, based on testing with a 10% formulation) and a trout early life stage NOAEC of 4.3 ppb , indicating a low potential for acute or chronic risk to fish.

Compared to other insecticides, while the risk represented by pyriproxyfen is limited to chronic effects to freshwater invertebrates, many other insecticides represent acute and chronic risks to several taxonomic groups. The ecosystem impact from pyriproxyfen are expected to be less than these other pesticides.

Endangered Species

Pyriproxyfen may affect endangered and threatened invertebrate species (crustacean and insect). The registrant should be required to provide information on the proximity of endangered aquatic invertebrates and terrestrial insects to the proposed use sites. They may gather this information independently or join the Endangered Species Task Force. This information will be used by the OPP Endangered Species Protection Program to develop recommendations to avoid adverse effects to Federally listed threatened or endangered species. See attachment 3 for list of endangered insects and crustacean species listed as occurring in counties where citrus, almonds, tomatoes and peppers are grown (actual lists are being provided electronically).

Adequacy of Data

Eco-Tox Data

The data were adequate to assess the risk to freshwater organisms, and estuarine fish species. However, acute and chronic risk to shrimp and mollusks could not be assessed. The original acute and chronic studies for shrimp and mollusks were not considered reliable.

The MRID numbers are:

Oyster Acute test: 448384-01
Mysid Acute test: 448384-05
Mysid life-cycle study: 448384-02

The registrant submitted two new acute studies, one for shrimp and one for mollusks; these are in review and cannot be completed in time for this assessment. The registrant also submitted additional information (raw data) on the original chronic shrimp life cycle study. However, the

main problem with the study, and the reason it was considered supplemental, was how the samples were prepared for chemical analysis. Because pyriproxyfen has a high Kow, the samples for analysis should have been centrifuged or filtered before analysis. By failing to do this, the concentration produced by the method would have included the chemical that was bound to any suspended organic materials in the solution and that could have produced higher concentrations than were actually in solution. If this happened, this would make the chemical appear less toxic than it actually was. This problem renders the study not upgradeable.

Without good shrimp and mollusk studies, EFED cannot assess risk to the organisms these test species represent. Citrus and tomatoes, especially, may be used in areas adjacent to estuaries. It is noteworthy that part of the basis for this being considered a preferable alternative is pyriproxyfen's presumed lower risk to nontarget organisms, including aquatic organisms. Lacking adequate estuarine invertebrate data leaves some uncertainty in that conclusion.

Environmental Fate Data

162-1. 1 Aerobic Soil Metabolism- MRID-43795502

This study is supplemental and upgradable. The Agency's (EFED) review of the above study indicated that the study can be upgraded with an adequate environmental chemistry method validation study including detection limits. However, the registrant's response to EFED contained only information concerning detection limits. Final conclusions about this study are pending validation of the chemistry method.

2. 163-1 Adsorption/Desorption- MRID-43795504

The study is supplemental and possibly upgradable. The Agency requires determination of material balances at all treatment levels. However, the study only provided material balances for samples at two treatment levels (10 and 50ng/g) for the soils tested. The Agency needs material balances at all treatment levels, in order to detect any losses of radioactivity that, e.g., could adhere to the sides of the laboratory glassware, or volatilize out of the testing system.

3. 164-1 MRIDs- 43795508, 43849813, 43849814, 44329503, 44329504. Terrestrial 43795502, 43795509 - Terrestrial Field Dissipation.

One California field dissipation study, MRID-43795509, was acceptable for partially satisfying the field dissipation requirement. Other acceptable representative field dissipation studies are recommended in other U.S. Agricultural areas to fully satisfy the requirement.

Reasons for rejecting most of the field dissipation studies were related to the inadequacy of the analytical method, for example, recoveries ranged from 59 to 100% - MRID -43849813; 6 of 28 recoveries were <70%.

None of the registrant's method modifications improved the recovery of PYPAC from soil. Two metabolites PYPAC and 4'-0h-Pyr identified in a previously reviewed aerobic metabolism study (MRID-43795502), were not detected at any sampling interval at either site. MRID 43849813, 14.

Because half of the recoveries during the PYPAC analytical procedures were below the acceptable 70 - 120% range, the reliability of the method is questionable.

Environmental Hazard Label Statement:

> "This pesticide is toxic to fish and aquatic invertebrates. Do not apply directly to water, or to areas where surface water is present or to intertidal areas below the mean high water mark. Drift and runoff from treated areas may be hazardous to aquatic organisms in neighboring areas. Do not contaminate water by cleaning of equipment washwaters or rinsate."

EFED recommends that the product label be amended to include "Avoid direct application and/or spray drift to bee hives"; until there is greater certainty that pyriproxyfen does not affect honey bee reproduction.

Attachment 1

PRZM3 Input File, odmflcit.inp (June 10 1999) jcl for pyriproxyfen
Location: Osceola County, FL.; Crop: citrus; MLRA 156A

```
  0.77   0.15      0  25.00      1      1
    4
  0.10   0.13   1.00   10.0           3   1.00   354.0
    1
    1   0.10  100.00   80.00      3  94  84  89    0.00  100.00
    1     3
0101 21 9 2209
0.10 0.10 0.10
.023 .023 .023
   36
 110548  170748  10848     1
 110549  170749  10849     1
 110550  170750  10850     1
 110551  170751  10851     1
 110552  170752  10852     1
 110553  170753  10853     1
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 110574  170774  10874     1
 110575  170775  10875     1
 110576  170776  10876     1
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110577 170777 10877 1
110578 170778 10878 1
110579 170779 10879 1
110580 170780 10880 1
110581 170781 10881 1
110582 170782 10882 1
110583 170783 10883 1
Application: 108 aerial appl. 0.123 kg a.i./ha @75% eff, w/5%drift
108 1 0 0
pryiproxyfen
010748 0 2 0.00 .123 0.75 0.05
150748 0 2 0.00 .123 0.75 0.05
290748 0 2 0.00 .123 0.75 0.05
010749 0 2 0.00 .123 0.75 0.05
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290767 0 2 0.00 .123 0.75 0.05
010768 0 2 0.00 .123 0.75 0.05
150768 0 2 0.00 .123 0.75 0.05
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150769 0 2 0.00 .123 0.75 0.05
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010770 0 2 0.00 .123 0.75 0.05
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010773 0 2 0.00 .123 0.75 0.05

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150777  0 2 0.00 .123 0.75 0.05
290777  0 2 0.00 .123 0.75 0.05
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010783  0 2 0.00 .123 0.75 0.05
150783  0 2 0.00 .123 0.75 0.05
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  0.     1
 0.00  0.000   0.50
```

Soil Series: Adamsville sand; Hydrogic Group C

```
 100.00        0  0  0  0  0  0  0  0  0
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    3
    1  10.000  1.440  0.086  0.000  0.000  0.000
       0.045  0.045  0.000
       0.100  0.086  0.036  0.580  156.0
    2  10.000  1.440  0.086  0.000  0.000  0.000
       0.045  0.045  0.000
```

```
    1.000  0.086  0.036  0.580  156.0
  3 80.000  1.580  0.030  0.000  0.000  0.000
    0.045  0.045  0.000
    5.000  0.030  0.023  0.116  156.0
  0
WATR  YEAR   10  PEST  YEAR   10  CONC  YEAR   10  1
  6
 11 -----
  5  DAY
RFLX  TSER  0  0  1.E5
EFLX  TSER  0  0  1.E5
ESLS  TSER  0  0  1.E0
RUNF  TSER  0  0  1.E0
PRCP  TSER  0  0  1.E0
```

Exam input file
Citrus Pyriproxyfen
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0.0000 0.0000 0.0000
0.0000 0.0000 0.0000 0.0000 0.0000 0.0000 0.0000 0.0000
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1.3753E-03 1.3753E-03 1.3753E-03 1.3753E-03
0.0000 0.0000 0.0000 0.0000
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0.0000 0.0000 0.0000 0.0000

Attachment 1b Output file for Citrus

Compound: Pyriproxyfen

Use: Citrus

Site: MLRA 156A - Florida Everglades and Associated Areas

Rate: 3 aerial applications @ 0.110 lb a.i./ac (w/ 5% drift)

Soil Type: Adamsville Sand (HSG: C)

Upper 10th percentile EECs (ug/L)

peak	96-hour	21-day	60-day	90-day	yearly
0.456	0.324	0.217	0.174	0.154	0.106

Mean of annual value: .096

Standard deviation of annual value: .013

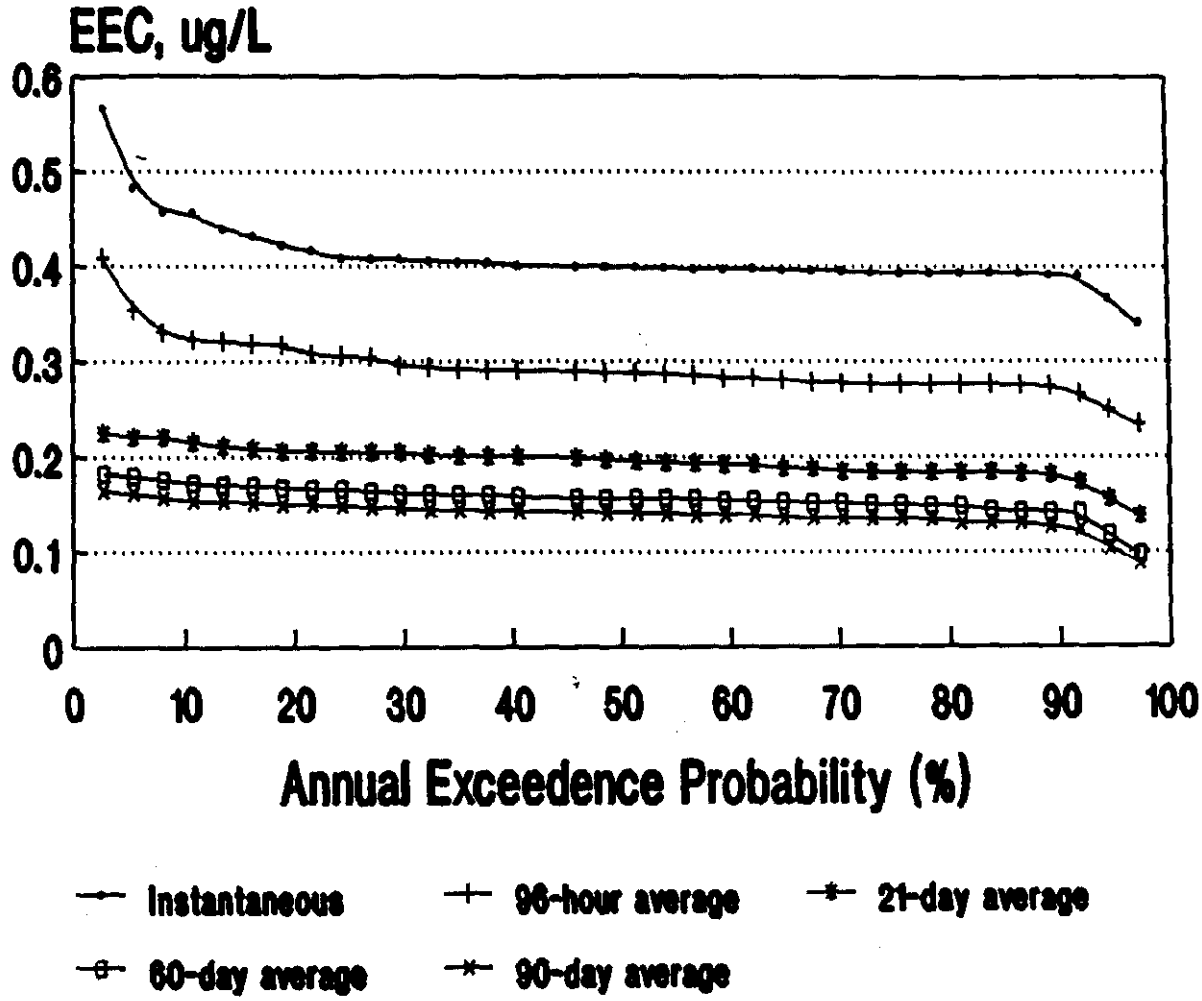
Upper 90% confidence limit of mean: .099

PRZM/EXAMS results of Pyriproxyfen use on citrus

WATER COLUMN DISSOLVED CONCENTRATION (PPB)

YEAR	PEAK	96 HOUR	21 DAY	60 DAY	90 DAY	YEARLY
1948	.340	.234	.138	.097	.088	.039
1949	.366	.249	.156	.118	.104	.064
1950	.392	.266	.174	.142	.124	.080
1951	.396	.274	.188	.150	.131	.087
1952	.432	.322	.206	.164	.144	.096
1953	.416	.293	.205	.168	.153	.103
1954	.439	.305	.205	.160	.144	.101
1955	.457	.318	.201	.152	.136	.097
1956	.391	.275	.182	.143	.131	.092
1957	.422	.291	.206	.182	.162	.105
1958	.404	.287	.194	.162	.146	.105
1959	.408	.289	.201	.166	.150	.104
1960	.399	.317	.201	.156	.148	.105
1961	.398	.282	.188	.152	.135	.097
1962	.393	.276	.184	.156	.139	.096
1963	.393	.276	.183	.144	.131	.092
1964	.397	.278	.184	.150	.139	.094
1965	.397	.320	.205	.157	.143	.100
1966	.404	.290	.199	.160	.142	.100
1967	.483	.330	.209	.170	.150	.103
1968	.399	.282	.221	.176	.157	.106
1969	.456	.353	.215	.172	.153	.108
1970	.400	.287	.192	.149	.135	.098
1971	.393	.277	.184	.149	.135	.094
1972	.405	.295	.211	.156	.139	.094
1973	.393	.276	.184	.156	.143	.098
1974	.395	.304	.195	.161	.143	.101
1975	.396	.290	.192	.154	.136	.096
1976	.393	.276	.184	.158	.141	.096
1977	.398	.286	.193	.154	.140	.097
1978	.393	.276	.185	.143	.127	.091
1979	.399	.280	.200	.153	.136	.092
1980	.407	.307	.221	.170	.152	.103
1981	.397	.285	.202	.180	.164	.112
1982	.408	.290	.197	.158	.141	.105
1983	.566	.408	.225	.166	.147	.102

EEC Plot - Pyriproxyfen Use on Citrus
Major Land Resource Area (MLRA): 156A
Florida Everglades and Associated Areas



Adamsville Sand (HSG: C)

ATTACHMENT 2

Discussion of Risk with Emphasis on Freshwater Invertebrates

The estimates of exposure used in the following discussion are based mostly on modeling done for previous proposed uses. EECs for peppers and tomatoes are based on modeling done for cotton, at the same application rate; EECs for almonds are based on modeling done for walnuts and pome fruits; citrus was modeled in this review for aquatic EECs..

The proposed pyriproxyfen uses on peppers, tomatoes, almonds and citrus are not expected to cause direct, adverse effects on mammals, birds, and freshwater and estuarine fish. Test results with *Daphnia magna* suggest no adverse acute effects and caused no adult mortality during the 21-day life-cycle test; however, production of young daphnids was strongly reduced. The duration of exposure necessary to reduce young production is unclear. The degree of reduced young production at the medium and higher test levels (50 to 80 percent) suggest that reproduction was affected very early in the study. Consequently risks were assessed using 96-hour and 21-day EECs to provide a range of effect levels, especially on the reduction in the number of young.

Using the dose-response curves from the daphnid life-cycle study (Appendix III) and the PRZM-EXAMS EECs for 21-day and 96-hour averages, reduction in the number of young was estimated to range from 50 to 70 percent and adult growth reduced by about a 9 to 14 percent (i.e., body length), respectively, following a single, maximum application to peppers and tomatoes. The duration of adverse effects of aquatic invertebrates would ap to be for a long period of time. The 1-year EEC exceeds the daphnid reproductive NOEC level and is expected to reduce invertebrate recruitment about 25 percent one year after treatment.

For three air-blast applications in almond and citrus orchards, the PRZM-EXAMS for 21-day and 96-hour averages indicate reductions of about 80 to 94 percent reduction in the number of young (recruitment) and about an 18 to 28 percent reduction in adult length, respectively.

It is difficult to estimate the number of aquatic invertebrate species which might be affected by pyriproxyfen use and the degree of the impact on their populations. A distribution of acute insecticidal sensitivities for various freshwater invertebrate species is very broad. Some species, such as stoneflies and mayflies are typically about 10 times more acutely sensitive to some chemicals than *Daphnia magna*, while other species, such as crayfish are less toxic. Based on the broad range of acute sensitivities, aquatic invertebrates might be expected to have a wide range of reproductive sensitivities. Since the daphnid reproductive risk quotients of 5.2 to 10 for peppers and tomatoes use and 13 to 30 for almonds and citrus uses are moderately high, the degree of risks suggests that the reproduction of a number of other aquatic invertebrate species would also be reduced. Aquatic invertebrate species most likely to be severely impacted would be sensitive species, such as stoneflies and mayflies that lay eggs during a short period of time shortly after a treatment.

Adverse effects on an aquatic ecosystem via trophic level interactions have been demonstrated in laboratory and field studies for some pesticides. It is unclear if and to what degree pyriproxyfen treatment-related reductions in aquatic invertebrate populations may produce indirect trophic effects on other aquatic species. Reductions in aquatic herbivorous invertebrates have been shown to produce strong adverse effects on algae and fish for some insecticides. For example, severe reductions in recruitment of aquatic invertebrate herbivores may reduce the amount of algae and phytoplankton grazed and produce algal blooms of varying degree depending on the severity of herbivore population reductions. Reductions of zooplankton and/or insect populations may affect the availability of food for fish and reduce fish growth, especially for juvenile fish. Insufficient data are available at this time to estimate effects on invertebrate populations and indirect trophic effects. In order to assess the number of species affected and the extent of those effects, aquatic microcosm studies would be needed to assess the extent on reproductive effects on invertebrate populations, as well as indirect effects of fish and algae.

Available test data on estuarine invertebrates were used to assess acute and chronic effects on estuarine invertebrates. However, there is uncertainty in the conclusions since the results from the estuarine invertebrate studies were found to be questionable. Because of the method of chemical analysis, the test concentrations, and thus the actual toxicity endpoints, are uncertain.

Acute (EC_{50} or LC_{50}) values to chronic toxicity values (expressed as reproductive EC_{50} values, estimated from dose-response curves) were compared for *Daphnia magna* and *Americamysis bahia*. Acutely, the mysid is more sensitive to pyriproxyfen than daphnids (67 ppb versus 400 ppb), but on a chronic basis daphnids were more sensitive than mysids (0.075 versus 2.7 ppb). For daphnids, the acute to chronic ratio for 50 percent effect levels is 5,333X (400 / 0.075 ppb) versus 25 X (67 / 2.7 ppb) for mysids. Traditional acute LC_{50} to chronic NOEC values are 26,667X (400 / 0.015 ppb) for daphnids versus 83X (67 / 0.81 ppb) for mysids. Analysis of the test results for the daphnid and mysid life-cycle studies indicate a identical pattern of effects. Adult mortality is non-existent or is within the range of control mortalities. The most sensitive endpoint is reduction in the number of young produced and lesser effects on adult growth for both species. Even the dose-response curves have similar reproductive effect slopes for both species. Both studies began with organisms less than 24 hours old and neither study showed chemically-related deaths occurring from ages of 1 day old to 22 days old and 29 days old. Consequently, the effects of reproduction must be occurring within a short period of time between fertilization and hatch, which is about three days for daphnids and maybe five days for mysids. If recruitment of young in these studies is effected by such a short time period, it is likely that short-term exposures of 4 to 9 days or less could produce the same reproductive effects as the 21-day and 28-day exposures in these studies. If reproduction is affected during a relatively short time period as suggested above, the use of the 96-hour EEC would be as valid, or possibly more so than the 21-day EEC to assess reproductive effects for these two species. Use of the two EEC values clearly provides for a range of risk quotients which would ap more appropriate than the 21-day EEC alone.

Attachment 3

Endangered Species Lists for Almonds, Citrus, Hot Peppers and Tomatoes provided in electronic form, if paper copy needed, please contact Dan Rieder, 703 305 5314

Attachment 4

013668

Date: **October 24, 1997**

MEMORANDUM

SUBJECT: ***PYRIPROXYFEN:*** - Report of the Hazard Identification Assessment Review Committee.

FROM: Jess Rowland
Branch Senior Scientist,
Science Analysis Branch, Health Effects Division (7509C)

THROUGH: K. Clark Swentzel, Chairman,
Hazard Identification Assessment Review Committee
Toxicology Branch II, Health Effects Division (7509C)
And
Mike Metzger, Co-Chairman
Hazard Identification Assessment Review Committee
Reregistration Action Branch 2, Health Effects Division (7509C)

TO: Rick Loranger
Branch Senior Scientist
Registration Action Branch 2
Health Effects Division (7509C)

PC Code: 129032

On October 14, 1997, the Health Effects Division's Hazard Identification Review committee met to evaluate the toxicology data base of Pyriproxyfen with special reference to the reproductive, developmental and neurotoxicity data. These data were re-reviewed specifically to address the sensitivity of infants and children from exposure to Pyriproxyfen as required by the Food Quality Protection Act (FQPA). In addition, the Committee also re-assessed the doses and endpoints selected for acute dietary, chronic dietary (RfD) as well as occupational and residential exposure risk assessments..

Committee Members in Attendance

Members in attendance were Karl Baetcke, William Burnam, Susan Makris, Nancy McCarroll, Melba Morrow, Kathleen Raffeale and Jess Rowland. Members in absentia were David Anderson and John Redden. Data was presented by William Dykstra of Toxicology Branch 1.

Data Presentation: _____
William Dykstra, Ph.D.

Report Preparation: _____
Jess Rowland, M.S

I. INTRODUCTION

On October 14, 1997, the Health Effects Division's Hazard Identification Review committee met to evaluate the toxicology data base of Pyriproxyfen with special reference to the reproductive, developmental and neurotoxicity data. These data were re-reviewed specifically to address the sensitivity of infants and children from exposure to Pyriproxyfen as required by the Food Quality Protection Act (FQPA). In addition, the Committee also re-assessed the doses and endpoints selected for acute dietary, chronic dietary (RfD) as well as occupational and residential exposure risk assessments.

II. HAZARD IDENTIFICATION

A. Acute Dietary (one-day)

Study Selected: None

MRID No. None

Executive Summary: None

Dose/Endpoint for Risk Assessment: Not Applicable

Comments about Study/Endpoint There were no effects observed in oral toxicology studies including the developmental toxicity studies in rats or rabbits that could be attributable to a single dose (exposure). Therefore, a dose and an endpoint was not selected for this risk assessment.

This risk assessment is NOT required

B. Chronic Dietary [Reference Dose (RfD)]

RfD Established in 1995:

Study Selected: Combined Chronic Toxicity/Carcinogenicity Study - Rat (§83 5)
90-Day Feeding Study - Rat (§82-1)

MRID No. 42178314, 43210501-03 (2-year study) 41321716 (90-Day)

Executive Summary: Groups of male and female Sprague-Dawley rats were fed diets containing Pyriproxyfen at 0, 120, 600 or 3000 ppm for 104 weeks. These doses were equivalent to 0, 5.42, 27.31 or 138 mg/kg/day in males and 0, 7.04, 35.1 or 182.7 mg/kg/day, in females, respectively. The NOEL was 35.1 mg/kg/day and the LOEL was 182.7 mg/kg/day based on a 16.9% decrease in body weight gain in females when

compared to controls. In males, the NOEL was greater than or equal to 138 mg/kg/day, the highest dose tested. Although the highest dose tested in males did not cause any toxicity and that the toxicity predicted in the 90 day study did not materialize in the long-term study, the RfD Committee concluded that repeating this study at higher doses would not provide additional information on either chronic toxicity or on the carcinogenic potential of Pyriproxyfen. Furthermore, a LOEL was established in females.

In a subchronic study, male and female Sprague-Dawley rats were fed diets containing Pyriproxyfen at 0, 400, 2000, 5000 or 10,000 ppm for 90 days. These doses were equivalent to 0, 23.49, 117.79, 309.05 or 641.8 mg/kg/day in males and 0, 27.68, 141.28, 356.30 or 783.96 mg/kg/day in females, respectively. The NOEL was 23.49 mg/kg/day in males and 27.68 mg/kg/day in females and the LOEL was 117.79 mg/kg/day in males and 141.28 mg/kg/day in females based on higher mean total cholesterol and phospholipids, decreased mean red blood cell, hematocrit and hemoglobin counts, and significantly higher relative liver weights.

Dose/Endpoint for establishing the RfD: Overall NOEL = 35.1 mg/kg/day based systemic toxicity observed in both the 90-day and 2-year studies (discussed above) at 141.28 mg/kg/day (LOEL).

Uncertainty Factor (UF): A UF of 100 was applied to account for inter (10 x)-and intra-(10 x) species variation.

$$\text{RfD} = \frac{\text{35.1 mg/kg/day (NOEL}}{\text{100 (UF)}} = \text{0.35 mg/kg/day}$$

The above RfD established in 1995 was re-assessed by this Committee pursuant to the FQPA and is discussed below:

Re-Assessment of the RfD : The Committee concurred with the endpoint, the dose and the UF of 100 used in 1995 and determined that the **10 x** factor to account for enhanced sensitivity of infants and children (as required by FQPA) **should be removed.** For chronic dietary risk assessment, **a UF of 100 is adequate** for the protection of this sub population from exposure to Pyriproxyfen. **Consequently, the RfD remains the same at 0.35 mg/kg/day.** A UF of 100 is adequate because.

(i) Developmental toxicity studies showed no increased sensitivity in fetuses as compared to maternal animals following *in utero* exposures in rats and rabbits.

(ii) A two generation reproduction toxicity study in rats showed no increased sensitivity in pups as compared to adults.

(iii) The toxicology data base is complete and there are no data gaps.

C. Occupational/Residential Exposure

1. Dermal Absorption

A dermal absorption study was not available for evaluation. Therefore, the Committee estimated a dermal absorption rate of **no more than 10% percent** based on the interpretation of data from oral and dermal studies in rats.

In the oral developmental toxicity study in rats, the NOEL was 100 mg/kg/day based on decreased body weight, body weight gain, and food consumption and increased water consumption at 300 mg/kg/day (LOEL).

In the dermal toxicity study in rats, no dermal or systemic toxicity was observed at the Limit-Dose of 1000 mg/kg/day.

In extrapolating from oral to dermal route, the Committee made the following assumptions: 1) that the toxicity seen via the oral route is due to direct transport of Pyriproxyfen from the absorption site to the target organs and 2) that metabolism following oral and dermal routes are similar. Under these assumption, no more than 10% (oral dose of 100 mg/kg/day / dermal dose 1000 mg/kg/day x 100) of Pyriproxyfen applied to the rat skin is absorbed without effects.

2. Short-Term Dermal - (1-7 days)

Study Selected: None

MRID No None

Executive Summary: None

Dose/Endpoint for Risk Assessment: Not Applicable

Comments about Study/Endpoint: No dermal or systemic toxicity was observed in the 21-day dermal toxicity study at the Limit-Dose of 1000 mg/kg/day. In addition, there were no effects observed in oral toxicity studies including the developmental toxicity studies in rats and rabbits that could be attributed to this time exposure period (1-7 days). Therefore, a dose and an endpoint was not identified for this risk assessment.

This risk assessment is NOT required.

3. Intermediate-Term Dermal (7 Days to Several Months)

Study Selected: None

MRID No None

Executive Summary: None

Dose/Endpoint for Risk Assessment: Not Applicable

Comments about Study/Endpoint: No dermal or systemic toxicity was observed in the 21-day dermal toxicity study at the Limit-Dose of 1000 mg/kg/day. In addition, there were no effects observed in oral toxicity studies including developmental toxicity studies in rats or rabbits that could be attributed to this exposure period. Therefore, a dose and an endpoint was not identified for this risk assessment.

This risk assessment is NOT required.

4. Long-Term Dermal (Several Months to Life-Time)

Study Selected: Combined Chronic Toxicity/Carcinogenicity Study - Rat (§83 5)
90-Day Feeding Study - Rat (§82-1)

MRID No. 42178314, 43210501-03 (2-year study) 41321716 (90-Day)

Executive Summary: Chronic Dietary (RfD)

Dose/Endpoint for Risk Assessment: Overall NOEL = 35.1 mg/kg/day based systemic toxicity observed in both the 90-day and 2-year studies (discussed under RfD) at 141.28 mg/kg/day (LOEL).

Comments about Study/Endpoint: The above dose was identified if chronic exposure via this route occurs. Since an oral dose was identified, a dermal absorption rate of **no more than 10%** should be used for risk assessments. This dose and endpoint was also used for establishing the RfD (chronic dietary risk assessment).

This risk assessment is required if chronic dermal exposure occurs .

5. Inhalation Exposure (Short- & Intermediate Term)

Study Selected: 28-Day Inhalation Toxicity (§82-4)

MRID No. 42178308

Executive Summary: In a 28-day study, groups of male and female Sprague-Dawley rats were exposed via inhalation at concentrations of 0, 269, 482, or 1000 mg/m^3 for four hours/day for 28 days. The NOEL was 482 mg/m^3 and the LOEL was 1000 mg/m^3 based on increased salivation. Sporadic decreases in body weight were also reported and a statistically significant increase was also reported in the lactate dehydrogenase (LDH) level. This increase was not considered to be biologically significant. In terms of mg/kg/dose, the NOEL was 138 mg/kg in males and 162 mg/kg in females.

Dose and Endpoint for Risk Assessment: Not Applicable

Comments About Study and/or End Point: Because of the lack of significant toxicological effects, the Committee determined that Short- and Intermediate term risk assessments via the inhalation route are not required. This is similar to the decisions made for not requiring Short-and Intermediate Term dermal risk assessment due to the lack of dermal or systemic toxicity at 1000 mg/kg/day in the 21-day dermal toxicity study in rats.

These risk assessments are NOT required.

6. Inhalation Exposure (Long-Term)

Study Selected: Combined Chronic Toxicity/Carcinogenicity Study - Rat (§83 5)
90-Day Feeding Study - Rat (§82-1)

MRID No. 42178314, 43210501-03 (2-year study) 41321716 (90-Day)

Executive Summary: Chronic Dietary (RfD)

Dose/Endpoint for Risk Assessment: Overall NOEL = 35.1 mg/kg/day based systemic toxicity observed in both the 90-day and 2-year studies (discussed under RfD) at 141.28 mg/kg/day (LOEL).

Comments About Study and/or End Point: The Committee selected a oral NOEL for this risk assessment because 1) the potential for long-term inhalation exposure; 2) the 28-day duration of exposure in the inhalation study discussed above is not an appropriate long-term exposure period; and 3) an oral dose was identified for Long-Term dermal risk assessments.

Since a oral NOEL was identified, risk assessment should be as follows:

e

(i) The inhalation exposure component (i.e., mg/L) using a 100 % absorption rate (default value) should be converted to a dose (mg/kg/day).

(ii) The dermal exposure componet (i.e, mg/kg/day) using 10% dermal absorptrion may be combined to this converted dose (mg/kg/day).

(iii) This dose should then be compared to the oral NOEL of 35.1 mg/kg/ day (systemic toxicity)to calculate the Margins of Exposure (MOE).

(iv) The dermal MOE and the inhalation MOE can not be combined since no common toxicological endpoints were seen via these routes.

D. Margin of Exposure for Occupational/Residential Exposures:

A Margin of Exposure of 100 is adequate to ensure protection from occupational and residential exposures to Pyriproxyfen by dermal and inhalation routes. A MOE of 100 is adequate because:

(i) Developmental toxicity studies showed no increased sensitivity to fetuses as compared to maternal animals following *in utero* exposures in rats and rabbits.

(ii) A two generation reproduction toxicity study in rats showed no increased sensitivity to pups as compared to adults and offsprings.

(iii) The toxicology data base is complete and there are no data gaps.

III. FQPA CONSIDERATIONS

1. Determination of Sensitivity

The oral perinatal and prenatal data demonstrated no indication of increased sensitivity of rats or rabbits to *in utero* exposure to Pyriproxyfen.

In a prenatal developmental toxicity study in Sprague-Dawley rats, Pyriproxyfen (97.2%) was administered at doses of 100, 300, or 1000 mg/kg/day by gavage in 5 mg/kg of corn oil on gestation days 7-17. The study was conducted in two segments. In one, the dams were killed on gestation day 21 and fetuses were evaluated, in the other, the dams delivered naturally and pups were weaned at postnatal day 21. Pups were killed serially at postnatal day 21 (after assessment of reflexes and sensory response), at 8 weeks of age (following open field testing, rotorod testing, and examination of learning ability in a water maze), or after assessment of reproductive performance. The maternal NOEL was 100 mg/kg/day, based upon decreased body weight, body weight gain, and food consumption and increased water consumption at the LOEL of 300 mg/kg/day. At 1000 mg/kg/day, increased incidences of mortality and clinical signs were also observed. The developmental NOEL was 300 mg/kg/day, based upon an increased incidence of skeletal variations at gestation day 21 and unspecified visceral variations at postnatal day 56.

> **NOTE: The DER has not been revised as recommended by the RfD Committee on 9/15/95. This Committee concurrs with the RfD Committee and recommends that the DER and the 1-Liner be revised as soon as possible.**

A prenatal developmental toxicity study was conducted in pregnant JW-NIBS rabbits, in which Pyriproxyfen (97.2%) was administered by gavage at doses of 100, 300, or 1000 mg/kg/day in distilled water on gestation days 6-18. The maternal NOEL was 100 mg/kg/day. The maternal LOEL was 300 mg/kg/day, based on the occurrence of premature delivery/abortions, soft stools, emaciation, lusterless fur, decreased activity, and bradypnea/deep breathing. At 1000 mg/kg/day, these signs increased in incidence and frequency. The developmental NOEL was 300 mg/kg/day, with an undetermined LOEL, since it could not be determined whether 1000 mg/kg/day was an effect level based on decreased viable litters available for examination (4). This was due to the abortions/premature deliveries and death in the does. [Nevertheless, the Committee recommended that the abortions be considered evidence of toxicity to the fetuses, and that the developmental LOEL be set at 1000 mg/kg/day, inspite of the overwhelming maternal toxicity] (MRID Nos.42178311, 43215401, 43215402, 41321720).

In a two-generation reproduction study, Pyriproxyfen (95.3%) was administered to Sprague-Dawley rats at dietary levels of 200, 1000, or 5000 ppm (18, 87, or 453 mg/kg/day for males and 20, 96, or 498 mg/kg/day for females). The parental NOEL was 1000 ppm (87/96 mg/kg/day for M/F) and the parental LOEL was 5000 ppm (453/498 mg/kg/day for M/F), based on decreased body weights, body weight gain, and food consumption in both sexes and generations, increased liver weight in F1 males and females, and histopathological changes in the liver and kidney of F1 males. There were no effects on reproduction (reproductive NOEL ≥5000 ppm). The NOEL for effects on the offspring was 1000 ppm (87/96 mg/kg/day for M/F) and the offspring LOEL was 5000 ppm (453/498 mg/kg/day for M/F), based on decreased body weights on lactation days 14 and 21. (The DER was not corrected per recommendations of the RfD Committee report of 9/15/95; however, the Committee determined that, in support of FQPA, the offspring toxicity should be described separately from "reproductive" toxicity) (MRID 42178313, Doc. No. 010682).

2. Recommendation for a Developmental Neurotoxicity Study:

The Committee determined that a developmental neurotoxicity study is not required. This was based upon a weight-of-the-evidence consideration of the following information:

Pyriproxyfen does not appear to be a neurotoxic chemical. There was no indication of toxicity to the central or peripheral nervous system in subchronic or chronic toxicity studies. No treatment-related alterations in brain weight or histopathology (non-perfused tissues) were observed following exposure to Pyriproxyfen.

No evidence of developmental anomalies of the fetal nervous system were observed in the prenatal developmental toxicity studies in either rats, or rabbits, at maternally toxic oral doses up to 1000 and 300 mg/kg/day, respectively.

No evidence of an effect on functional developmental was observed in a postnatal segment of the developmental study in rats

IV. DATA GAP

None